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Celgene Corporation*

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

CELGENE CORPORATION,

Plaintiff,

v.

APOTEX INC.,

Defendant.

Civil Action No. _____

**COMPLAINT FOR
PATENT INFRINGEMENT**

(Filed Electronically)

Plaintiff Celgene Corporation (“Celgene”), by its undersigned attorneys, for its Complaint against defendant Apotex Inc. (“Defendant” or “Apotex Inc.”), alleges as follows:

Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq.*, arising from Apotex Inc.’s filing of an Abbreviated New Drug Application (“ANDA”) No. 211022 (“Apotex’s ANDA”) with the United States Food and Drug Administration (“FDA”) seeking approval to commercially market generic versions of Celgene’s 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg REVLIMID[®] drug products (“Apotex’s ANDA Products”) prior to the expiration of United States Patent Nos. 6,315,720 (“the ’720 patent”); 6,561,977 (“the ’977 patent”); 6,755,784 (“the ’784 patent”); 8,315,886 (“the ’886 patent”); 8,626,531 (“the ’531 patent”); 7,465,800 (“the ’800 patent”); 7,855,217 (“the ’217 patent”);

7,468,363 (“the ’363 patent”); and 8,741,929 (“the ’929 patent”), all owned by Celgene (collectively, “the patents-in-suit”).

The Parties

2. Plaintiff Celgene is a biopharmaceutical company committed to improving the lives of patients worldwide. Celgene focuses on, and invests heavily in, the discovery and development of products for the treatment of severe and life-threatening conditions. Celgene is a world leader in the treatment of many such diseases, including cancer. Celgene is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 86 Morris Avenue, Summit, New Jersey 07901.

3. On information and belief, Defendant Apotex Inc. is a corporation organized and existing under the laws of Canada, having a principal place of business at 150 Signet Drive, Toronto, Ontario M9L 1T9, Canada.

The Patents-in-Suit

4. On November 13, 2001, the United States Patent and Trademark Office (“USPTO”) duly and lawfully issued the ’720 patent, entitled, “Methods for delivering a drug to a patient while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug,” to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the ’720 patent is attached hereto as Exhibit A.

5. On May 13, 2003, the USPTO duly and lawfully issued the ’977 patent, entitled, “Methods for delivering a drug to a patient while restricting access to the drug by patients for whom the drug may be contraindicated,” to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the ’977 patent is attached hereto as Exhibit B.

6. On June 29, 2004, the USPTO duly and lawfully issued the ’784 patent, entitled, “Methods for delivering a drug to a patient while restricting access to the drug by patients for

whom the drug may be contraindicated,” to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the ’784 patent is attached hereto as Exhibit C.

7. On November 20, 2012, the USPTO duly and lawfully issued the ’886 patent, entitled, “Methods for delivering a drug to a patient while restricting access to the drug by patients for whom the drug may be contraindicated,” to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the ’886 patent is attached hereto as Exhibit D.

8. On January 7, 2014, the USPTO duly and lawfully issued the ’531 patent, entitled “Methods for delivering a drug to a patient while restricting access to the drug by patients from whom the drug may be contraindicated,” to Celgene as assignee of the inventors Bruce A. Williams and Joseph K. Kaminski. A copy of the ’531 patent is attached hereto as Exhibit E.

9. On December 16, 2008, the USPTO duly and lawfully issued the ’800 patent, entitled, “Polymorphic Forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione,” to Celgene as assignee of the inventors Markian S. Jaworsky, Roger Shen-Chu Chen, and George W. Muller. A copy of the ’800 patent is attached hereto as Exhibit F.

10. On December 21, 2010, the USPTO duly and lawfully issued the ’217 patent, entitled, “Polymorphic Forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione,” to Celgene as assignee of the inventors Markian S. Jaworsky, Roger Shen-Chu Chen, and George W. Muller. A copy of the ’217 patent is attached hereto as Exhibit G.

11. On December 23, 2008, the USPTO duly and lawfully issued the ’363 patent, entitled, “Methods for treatment of cancers using 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione,” to Celgene as assignee of inventor Jerome B. Zeldis. A copy of the ’363 patent is attached hereto as Exhibit H.

12. On June 3, 2014, the USPTO duly and lawfully issued the '929 patent, entitled, "Methods using 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for the treatment of mantle cell lymphomas," to Celgene as assignee of inventor Jerome B. Zeldis. A copy of the '929 patent is attached hereto as Exhibit I.

The REVLIMID[®] Drug Product

13. Celgene holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for lenalidomide capsules (NDA No. 21-880), which it sells under the trade name REVLIMID[®].

14. The claims of the patents-in-suit cover, *inter alia*, lenalidomide, solid forms of lenalidomide, pharmaceutical compositions containing lenalidomide, and systems and methods of use and administration of lenalidomide or pharmaceutical compositions containing lenalidomide.

15. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the patents-in-suit are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to REVLIMID[®].

16. The labeling for REVLIMID[®] instructs and encourages physicians, pharmacists, and other healthcare workers and patients to administer REVLIMID[®] according to one or more of the methods claimed in the patents-in-suit.

Jurisdiction and Venue

17. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

18. On information and belief, Apotex Inc. is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District.

On information and belief, this Judicial District will be a destination for the generic drug product described in Apotex's ANDA. On information and belief, Apotex Inc. prepares and/or aids in the preparation and submission of ANDAs to the FDA.

19. This Court also has personal jurisdiction over Apotex Inc. because Apotex Inc. has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Apotex Inc. regularly and continuously transacts business within New Jersey, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey. On information and belief, Apotex Inc. derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey. For example, Apotex's website states it "has many submissions for U.S. regulatory review as well as being a leader for generic drug approvals." About Apotex, <http://www.apotex.com/ca/en/about/video.asp> (last accessed January 10, 2018). On information and belief, Apotex Inc. derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

20. This Court has personal jurisdiction over Apotex Inc. because, *inter alia*, it: (1) has purposely availed itself of the privilege of doing business in New Jersey, including directly or indirectly through its subsidiary, agent, and/or alter ego, Apotex Corp., a company registered with the State of New Jersey as a drug wholesaler under Registration No. 5003192; and (2) maintains extensive and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey, including through, directly or indirectly, Apotex Corp. On information and belief, Apotex Corp. acts at the direction, and for the benefit, of Apotex Inc., and is controlled and/or dominated by Apotex Inc.

21. This Court has personal jurisdiction over Apotex Inc. by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. On information and belief, Apotex Inc. purposefully has conducted and continues to conduct business in this Judicial District.

22. This Court has personal jurisdiction over Apotex Inc. because, *inter alia*, it has committed an act of patent infringement under 35 U.S.C. § 271(e)(2), and has sent notice of that infringement to Celgene in the State of New Jersey. On information and belief, Apotex Inc. intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will continue to lead to foreseeable harm and injury to Celgene in New Jersey and in this Judicial District. For example, on information and belief, Apotex Inc. will work alone or in concert with Apotex Corp. and/or other subsidiaries towards the regulatory approval, manufacturing, use, importation, marketing, sale, offer for sale, and distribution of generic pharmaceutical products, including Apotex's ANDA Products, throughout the United States, including in New Jersey and in this Judicial District, prior to the expiration of the patents-in-suit.

23. On information and belief, Apotex Inc. has previously invoked, stipulated, and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

24. Apotex Inc. has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey, and has not challenged personal jurisdiction. *See, e.g., Mitsubishi Tanabe Pharma Corporation, et al. v. Apotex Inc., et al.*, Civil Action No. 17-5278 (PGS)(DEA) (D.N.J.); *Celgene Corp. v. Hetero Labs Ltd., et al.*, Civil Action No. 17-3387 (ES)(MAH) (D.N.J.); *AstraZeneca AB, et al. v. Apotex Corp., et al.*, Civil Action No. 15-8492 (FLW)(DEA) (D.N.J.); *Bausch & Lomb Inc., et al. v. Apotex Inc., et al.*, Civil Action No. 15-3879 (NLH)(JS) (D.N.J.); *Novartis Pharm. Corp. v.*

Apotex Inc., et al., Civil Action No. 15-3634 (SDW)(LDW) (D.N.J.); *Merck Sharp & Dohme Corp. v. Apotex Inc., et al.*, Civil Action No. 15-2384 (PGS)(TJB) (D.N.J.).

25. Apotex Inc. has further availed itself of the jurisdiction of this Court by initiating litigation in this Judicial District. *See, e.g., Apotex Inc. v. Shire LLC*, Civil Action No. 08-3598 (SRC)(MAS) (D.N.J.); *Apotex Inc., et al. v. Pharmaceutical Resources, Inc.*, Civil Action No. 06-1153 (JLL)(MF) (D.N.J.).

26. In the alternative, this Court has personal jurisdiction over Apotex Inc. because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Celgene's claims arise under federal law; (b) Apotex Inc. is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Apotex Inc. has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Apotex Inc. satisfies due process.

27. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and/or 1400(b).

Acts Giving Rise To This Suit

28. Pursuant to Section 505 of the FFDCA, Apotex Inc. filed Apotex's ANDA seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Apotex's ANDA Products, before the patents-in-suit expire.

29. On information and belief, following FDA approval of Apotex's ANDA, Apotex Inc. will make, use, sell, or offer to sell Apotex's ANDA Products throughout the United States, or import such generic products into the United States.

30. On information and belief, in connection with the filing of its ANDA as described above, Apotex Inc. provided a written certification to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (“Apotex’s Paragraph IV Certification”), alleging that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Apotex’s ANDA.

31. No earlier than November 28, 2017, Apotex Inc. sent written notice of its Paragraph IV Certification to Celgene (“Apotex’s Notice Letter”). Apotex’s Notice Letter alleges that the claims of the patents-in-suit are invalid and/or will not be infringed by the activities described in Apotex’s ANDA. Apotex’s Notice Letter also informed Celgene that Apotex seeks approval to market Apotex’s ANDA Products before the patents-in-suit expire. Apotex Inc. specifically directed Apotex’s Notice Letter to Celgene’s headquarters in Summit, New Jersey, in this Judicial District.

Count I
(Infringement of the ’720 Patent)

32. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

33. Apotex Inc.’s submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Apotex’s ANDA Products, prior to the expiration of the ’720 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

34. There is a justiciable controversy between the parties hereto as to the infringement of the ’720 patent.

35. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will infringe one or more claims of the '720 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States.

36. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will induce infringement of one or more claims of the '720 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, upon FDA approval of Apotex's ANDA, Apotex Inc. will intentionally encourage acts of direct infringement with knowledge of the '720 patent and knowledge that its acts are encouraging infringement.

37. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will contributorily infringe one or more claims of the '720 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, Apotex Inc. has had and continues to have knowledge that Apotex's ANDA Products are especially adapted for a use that infringes one or more claims of the '720 patent and that there is no substantial non-infringing use for Apotex's ANDA Products.

38. Celgene will be substantially and irreparably damaged and harmed if Apotex Inc.'s infringement of the '720 patent is not enjoined.

39. Celgene does not have an adequate remedy at law.

40. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count II
(Infringement of the '977 Patent)

41. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

42. Apotex Inc.'s submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Apotex's ANDA Products, prior to the expiration of the '977 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

43. There is a justiciable controversy between the parties hereto as to the infringement of the '977 patent.

44. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will infringe one or more claims of the '977 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States.

45. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will induce infringement of one or more claims of the '977 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, upon FDA approval of Apotex's ANDA, Apotex Inc. will intentionally encourage acts of direct infringement with knowledge of the '977 patent and knowledge that its acts are encouraging infringement.

46. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will contributorily infringe one or more claims of the '977 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, Apotex Inc. has had and continues to have knowledge that Apotex's ANDA Products are especially adapted for a use that infringes one or more claims

of the '977 patent and that there is no substantial non-infringing use for Apotex's ANDA Products.

47. Celgene will be substantially and irreparably damaged and harmed if Apotex Inc.'s infringement of the '977 patent is not enjoined.

48. Celgene does not have an adequate remedy at law.

49. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count III
(Infringement of the '784 Patent)

50. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

51. Apotex Inc.'s submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Apotex's ANDA Products, prior to the expiration of the '784 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

52. There is a justiciable controversy between the parties hereto as to the infringement of the '784 patent.

53. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will infringe one or more claims of the '784 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States.

54. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will induce infringement of one or more claims of the '784 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, upon FDA approval of Apotex's ANDA, Apotex Inc.

will intentionally encourage acts of direct infringement with knowledge of the '784 patent and knowledge that its acts are encouraging infringement.

55. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will contributorily infringe one or more claims of the '784 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, Apotex Inc. has had and continues to have knowledge that Apotex's ANDA Products are especially adapted for a use that infringes one or more claims of the '784 patent and that there is no substantial non-infringing use for Apotex's ANDA Products.

56. Celgene will be substantially and irreparably damaged and harmed if Apotex Inc.'s infringement of the '784 patent is not enjoined.

57. Celgene does not have an adequate remedy at law.

58. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IV
(Infringement of the '886 Patent)

59. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

60. Apotex Inc.'s submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Apotex's ANDA Products, prior to the expiration of the '886 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

61. There is a justiciable controversy between the parties hereto as to the infringement of the '886 patent.

62. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will infringe one or more claims of the '886 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States.

63. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will induce infringement of one or more claims of the '886 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, upon FDA approval of Apotex's ANDA, Apotex Inc. will intentionally encourage acts of direct infringement with knowledge of the '886 patent and knowledge that its acts are encouraging infringement.

64. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will contributorily infringe one or more claims of the '886 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, Apotex Inc. has had and continues to have knowledge that Apotex's ANDA Products are especially adapted for a use that infringes one or more claims of the '886 patent and that there is no substantial non-infringing use for Apotex's ANDA Products.

65. Celgene will be substantially and irreparably damaged and harmed if Apotex Inc.'s infringement of the '886 patent is not enjoined.

66. Celgene does not have an adequate remedy at law.

67. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count V
(Infringement of the '531 Patent)

68. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

69. Apotex Inc.'s submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Apotex's ANDA Products, prior to the expiration of the '531 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

70. There is a justiciable controversy between the parties hereto as to the infringement of the '531 patent.

71. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will infringe one or more claims of the '531 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States.

72. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will induce infringement of one or more claims of the '531 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, upon FDA approval of Apotex's ANDA, Apotex Inc. will intentionally encourage acts of direct infringement with knowledge of the '531 patent and knowledge that its acts are encouraging infringement.

73. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will contributorily infringe one or more claims of the '531 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, Apotex Inc. has had and continues to have knowledge that Apotex's ANDA Products are especially adapted for a use that infringes one or more claims

of the '886 patent and that there is no substantial non-infringing use for Apotex's ANDA Products.

74. Celgene will be substantially and irreparably damaged and harmed if Apotex Inc.'s infringement of the '531 patent is not enjoined.

75. Celgene does not have an adequate remedy at law.

76. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VI
(Infringement of the '800 Patent)

77. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

78. Apotex Inc.'s submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Apotex's ANDA Products, prior to the expiration of the '800 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

79. There is a justiciable controversy between the parties hereto as to the infringement of the '800 patent.

80. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will infringe one or more claims of the '800 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States.

81. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will induce infringement of one or more claims of the '800 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, upon FDA approval of Apotex's ANDA, Apotex Inc.

will intentionally encourage acts of direct infringement with knowledge of the '800 patent and knowledge that its acts are encouraging infringement.

82. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will contributorily infringe one or more claims of the '800 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, Apotex Inc. has had and continues to have knowledge that Apotex's ANDA Products are especially adapted for a use that infringes one or more claims of the '800 patent and that there is no substantial non-infringing use for Apotex's ANDA Products.

83. Celgene will be substantially and irreparably damaged and harmed if Apotex Inc.'s infringement of the '800 patent is not enjoined.

84. Celgene does not have an adequate remedy at law.

85. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VII
(Infringement of the '217 Patent)

86. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

87. Apotex Inc.'s submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Apotex's ANDA Products, prior to the expiration of the '217 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

88. There is a justiciable controversy between the parties hereto as to the infringement of the '217 patent.

89. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will infringe one or more claims of the '217 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States.

90. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will induce infringement of one or more claims of the '217 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, upon FDA approval of Apotex's ANDA, Apotex Inc. will intentionally encourage acts of direct infringement with knowledge of the '217 patent and knowledge that its acts are encouraging infringement.

91. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will contributorily infringe one or more claims of the '217 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, Apotex Inc. has had and continues to have knowledge that Apotex's ANDA Products are especially adapted for a use that infringes one or more claims of the '217 patent and that there is no substantial non-infringing use for Apotex's ANDA Products.

92. Celgene will be substantially and irreparably damaged and harmed if Apotex Inc.'s infringement of the '217 patent is not enjoined.

93. Celgene does not have an adequate remedy at law.

94. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count VIII
(Infringement of the '363 Patent)

95. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

96. Apotex Inc.'s submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Apotex's ANDA Products, prior to the expiration of the '363 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

97. There is a justiciable controversy between the parties hereto as to the infringement of the '363 patent.

98. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will infringe one or more claims of the '363 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States.

99. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will induce infringement of one or more claims of the '363 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, upon FDA approval of Apotex's ANDA, Apotex Inc. will intentionally encourage acts of direct infringement with knowledge of the '363 patent and knowledge that its acts are encouraging infringement.

100. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will contributorily infringe one or more claims of the '363 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, Apotex Inc. has had and continues to have knowledge that Apotex's ANDA Products are especially adapted for a use that infringes one or more claims

of the '363 patent and that there is no substantial non-infringing use for Apotex's ANDA Products.

101. Celgene will be substantially and irreparably damaged and harmed if Apotex Inc.'s infringement of the '363 patent is not enjoined.

102. Celgene does not have an adequate remedy at law.

103. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

Count IX
(Infringement of the '929 Patent)

104. Celgene repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

105. Apotex Inc.'s submission of its ANDA to engage in the commercial manufacture, use, sale, offer for sale, or importation into the United States of Apotex's ANDA Products, prior to the expiration of the '929 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

106. There is a justiciable controversy between the parties hereto as to the infringement of the '929 patent.

107. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will infringe one or more claims of the '929 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States.

108. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will induce infringement of one or more claims of the '929 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, upon FDA approval of Apotex's ANDA, Apotex Inc.

will intentionally encourage acts of direct infringement with knowledge of the '929 patent and knowledge that its acts are encouraging infringement.

109. Unless enjoined by this Court, upon FDA approval of Apotex's ANDA, Apotex Inc. will contributorily infringe one or more claims of the '929 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Apotex's ANDA Products in the United States. On information and belief, Apotex Inc. has had and continues to have knowledge that Apotex's ANDA Products are especially adapted for a use that infringes one or more claims of the '929 patent and that there is no substantial non-infringing use for Apotex's ANDA Products.

110. Celgene will be substantially and irreparably damaged and harmed if Apotex Inc.'s infringement of the '929 patent is not enjoined.

111. Celgene does not have an adequate remedy at law.

112. This case is an exceptional one, and Celgene is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Celgene respectfully requests the following relief:

(A) A Judgment that Apotex Inc. has infringed the patents-in-suit by submitting ANDA No. 211022;

(B) A Judgment that Apotex Inc. has infringed, and that Apotex Inc.'s making, using, selling, offering to sell, or importing Apotex's ANDA Products will infringe one or more claims of the patents-in-suit;

(C) An Order that the effective date of FDA approval of ANDA No. 211022 be a date which is not earlier than the later of the expiration of the patents-in-suit, or any later expiration of exclusivity to which Celgene is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Apotex Inc. and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, selling, offering to sell, or importing Apotex's ANDA Products until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Celgene is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Apotex Inc., its officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any compounds, solid forms of lenalidomide, compositions, or methods as claimed in the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of the patents-in-suit, or any later expiration of exclusivity to which Celgene is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Apotex's ANDA Products will directly infringe, induce and/or contribute to infringement of the patents-in-suit;

(G) To the extent that Apotex Inc. has committed any acts with respect to the compounds, solid forms of lenalidomide, compositions, or methods claimed in the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Celgene damages for such acts;

(H) If Apotex Inc. engages in the commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Apotex's ANDA Products prior to the expiration of the patents-in-suit, a Judgment awarding damages to Celgene resulting from such infringement, together with interest;

(I) A Judgment declaring that the patents-in-suit remain valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding Celgene its attorneys' fees incurred in this action;

(K) A Judgment awarding Celgene its costs and expenses incurred in this action; and

(L) Such further and other relief as this Court may deem just and proper.

Dated: January 11, 2018

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CERTIFICATION PURSUANT TO L. CIV. R. 11.2 & 40.1

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matter captioned *Celgene Corporation v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 16-7704 (SDW)(LDW) (D.N.J.) is related to the matter in controversy because the matter in controversy involves the same plaintiff and some of the same patents, and because Apotex Inc. is seeking FDA approval to market generic versions of the same pharmaceutical product.

I further certify that the matter captioned *Celgene Corporation v. Zydus Pharmaceuticals (USA) Inc., et al.*, Civil Action No. 17-2528 (SDW)(LDW) (D.N.J.) is related to the matter in controversy because the matter in controversy involves the same plaintiff and some of the same patents, and because Apotex Inc. is seeking FDA approval to market generic versions of the same pharmaceutical product.

I further certify that the matter captioned *Celgene Corporation v. Dr. Reddy's Laboratories, Ltd., et al.*, Civil Action No. 17-5314 (SDW)(LDW) (D.N.J.) is related to the matter in controversy because the matter in controversy involves the same plaintiff, and because Apotex Inc. is seeking FDA approval to market generic versions of the same pharmaceutical product.

I further certify that the matter captioned *Celgene Corporation v. Cipla Ltd*, Civil Action No. 17-6163 (SDW)(LDW) (D.N.J.) is related to the matter in controversy because the matter in controversy involves the same plaintiff and some of the same patents, and because Apotex Inc. is seeking FDA approval to market generic versions of the same pharmaceutical product.

I further certify that the matter captioned *Celgene Corporation v. Lotus Pharm. Co., et al.*, Civil Action No. 17-6842 (SDW)(LDW) (D.N.J.) is related to the matter in controversy because the matter in controversy involves the same plaintiff and some of the same patents, and

because Apotex Inc. is seeking FDA approval to market generic versions of the same pharmaceutical product.

I further certify that the matter captioned *Celgene Corporation. v. Hetero Laboratories Limited, et al.*, Civil Action No. 17-3387 (ES)(MAH) (D.N.J.) is related to the matter in controversy because the matter in controversy involves the plaintiff in this action and some of the same patents, but it does not involve the same pharmaceutical product.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: January 11, 2018

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EXHIBIT A



US006315720B1

(12) **United States Patent**
Williams et al.

(10) **Patent No.:** **US 6,315,720 B1**
(45) **Date of Patent:** **Nov. 13, 2001**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE AVOIDING THE OCCURRENCE OF AN ADVERSE SIDE EFFECT KNOWN OR SUSPECTED OF BEING CAUSED BY THE DRUG**

(75) Inventors: **Bruce A. Williams**, Flemington;
Joseph K. Kaminski, Hampton, both of NJ (US)

(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/694,217**

(22) Filed: **Oct. 23, 2000**

(51) **Int. Cl.**⁷ **A61B 5/00**
(52) **U.S. Cl.** **600/300; 235/375**
(58) **Field of Search** 600/300, 304,
600/551; 395/202–210; 128/630; 706/23,
2, 3; 235/375

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,299,121 3/1994 Brill et al. 600/301
5,594,637 * 1/1997 Eisenberg et al. 395/202
5,619,991 * 4/1997 Sloane 128/630
5,660,176 8/1997 Iliff 600/300

5,845,255 12/1998 Mayaud 705/3
6,014,631 1/2000 Teagarden et al. 705/3
6,045,501 * 4/2000 Elsayed et al. 600/300
6,055,507 4/2000 Cunningham 705/3
6,063,026 * 5/2000 Schauss et al. 600/300
6,128,620 10/2000 Pissanos et al. 707/102
6,131,090 * 10/2000 Basso, Jr. et al. 706/23
6,202,923 * 3/2001 Boyer et al. 235/375

* cited by examiner

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(57) **ABSTRACT**

Improved methods for delivering to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug are disclosed. The methods are of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber, pharmacy and patient have been properly registered in the medium before the patient is approved to receive the drug. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to the side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

32 Claims, No Drawings

**METHODS FOR DELIVERING A DRUG TO A
PATIENT WHILE AVOIDING THE
OCCURRENCE OF AN ADVERSE SIDE
EFFECT KNOWN OR SUSPECTED OF
BEING CAUSED BY THE DRUG**

FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to fetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated

individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

- a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
- b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;

- c. in response to the information set, assigning the patient to at least one of the risk groups; and
- d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term “drug,” as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term “side effect” refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term “likely to arise” means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term “prescriber” refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term “contraindicated” refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered “contraindicated,” as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term “substantially,” as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for

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example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become regis-

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tered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or

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the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side

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effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is

contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenecity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of

child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional

pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female

patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

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As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacies who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has

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been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuberculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be

generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled

regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the

patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bio-availability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper

dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

1. In a method for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by said drug, wherein said method is of the type in which prescriptions for said drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in said medium and qualified to prescribe said drug, that the pharmacy is registered in said medium and qualified to fill the prescription for said drug, and the patient is registered in said medium and approved to receive said drug, the improvement comprising:

- a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for said drug;
- b. defining a set of information to be obtained from said patient, which information is probative of the risk that said adverse side effect is likely to occur if said drug is taken by said patient;
- c. in response to said information set, assigning said patient to at least one of said risk groups and entering said risk group assignment in said medium;
- d. based upon said information and said risk group assignment, determining whether the risk that said adverse side effect is likely to occur is acceptable; and
- e. upon a determination that said risk is acceptable, generating a prescription approval code to be retrieved by said pharmacy before said prescription is filled.

2. The method of claim 1 wherein, in response to said risk group assignment, said patient is counseled as to the risks of taking said drug and advised as to risk avoidance measures.

3. The method of claim 2 wherein said counseling comprises full disclosure of said risks.

4. The method of claim 3 wherein said prescription is filled only following said full disclosure and informed consent of said patient.

5. The method of claim 4 wherein said risk group assignment and said informed consent is verified by said prescriber at the time that said patient is registered in said computer readable storage medium.

6. The method of claim 5 wherein said risk group assignment and said informed consent is transmitted to said computer readable storage medium by facsimile and interpreted by optical character recognition software.

7. The method of claim 1 wherein said set of information includes the results of diagnostic testing.

8. The method of claim 7 wherein said diagnostic testing is probative of the onset of said adverse side effect.

9. The method of claim 7 wherein said diagnostic testing is probative of the concentration of said drug in a tissue of said patient.

10. The method of claim 7 wherein said diagnostic testing comprises genetic testing.

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11. The method of claim 1 wherein said side effect is likely to arise in said patient.

12. The method of claim 1 wherein said side effect is likely to arise in a foetus carried by said patient.

13. The method of claim 1 wherein said side effect is likely to arise in a recipient or a foetus carried by a recipient of the bodily fluid of said patient.

14. The method of claim 13 wherein said recipient is a sexual partner of said patient.

15. The method of claim 1 further comprising:

- f. defining for each said risk group a second set of information to be collected from said patient on a periodic basis;
- g. obtaining said second set of information from said patient; and
- h. entering said second set of information in said medium before said patient is approved to receive said drug.

16. The method of claim 15 wherein said second set of information comprises a survey regarding said patient's behavior and compliance with said risk avoidance measures.

17. The method of claim 16 wherein said survey is conducted telephonically using an integrated voice response system.

18. The method of claim 16 wherein said patient is a female of childbearing potential and said second set of information comprises the results of a pregnancy test.

19. The method of claim 18 wherein said periodic interval comprises about 28 days.

20. The method of claim 1 further comprising providing said patient with a contraceptive device or formulation.

21. The method of claim 1 wherein said adverse side effect comprises a teratogenic effect.

22. The method of claim 1 wherein said drug is thalidomide.

23. The method of claim 21 wherein said teratogenic effect is likely to arise in a foetus carried by said patient.

24. The method of claim 21 wherein said teratogenic effect is likely to arise in a foetus carried by a recipient of the bodily fluid of said patient.

25. The method of claim 24 wherein said recipient of the bodily fluid of said patient is a sexual partner of said patient.

26. The method of claim 21 wherein said set of information includes the results of a pregnancy test.

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27. The method of claim 26 wherein said prescription is filled for no more than about 28 days.

28. In a method for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by said drug, wherein said method is of the type in which prescriptions for said drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in said medium and qualified to prescribe said drug, that the pharmacy is registered in said medium and qualified to fill the prescription for said drug, and the patient is registered in said medium and approved to receive said drug, the improvement comprising:

- a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for said drug;
- b. defining a set of information to be obtained from said patient, which information is probative of the risk that said adverse side effect is likely to occur if said drug is taken by said patient;
- c. in response to said information set, assigning said patient to at least one of said risk groups and entering said risk group assignment in said medium;
- d. based upon said information and said risk group assignment, determining whether the risk that said adverse side effect is likely to occur is acceptable; and
- e. upon a determination that said risk is acceptable, generating a prescription approval code to be retrieved by said pharmacy before said prescription is filled,

wherein said adverse side effect is likely to arise in patients who take said drug in combination with at least one other drug.

29. The method of claim 28 wherein said set of information is also probative of the likelihood that said patient may take said drug and said other drug in combination.

30. The method of claim 28 wherein said set of information includes the results of diagnostic testing.

31. The method of claim 30 wherein said diagnostic testing comprises testing for evidence of the use of said other drug.

32. The method of claim 30 wherein said diagnostic testing comprises testing for evidence which is indicative of the onset of said adverse side effect.

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EXHIBIT B



US006561977B2

(12) **United States Patent**
Williams et al.

(10) **Patent No.:** **US 6,561,977 B2**
(45) **Date of Patent:** ***May 13, 2003**

(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(51) **Int. Cl.**⁷ **A61B 5/00**; G06F 17/00

(52) **U.S. Cl.** **600/300**; 128/920; 235/375; 705/3; 702/19

(58) **Field of Search** 600/300–301, 600/304, 551; 395/202–210; 706/23, 2–3; 705/2–4; 735/375; 707/102

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,299,121 A 3/1994 Brill et al.

5,594,637 A 1/1997 Eisenberg et al.
5,619,991 A 4/1997 Sloane
5,660,176 A 8/1997 Iliff
5,845,255 A 12/1998 Mayaud
5,974,203 A 10/1999 Tadokoro et al.
6,014,631 A 1/2000 Teagarden et al.
6,045,501 A * 4/2000 Elsayed et al. 600/300
6,055,507 A 4/2000 Cunningham
6,063,026 A * 5/2000 Schauss et al. 600/300
6,128,620 A 10/2000 Pissanos et al.
6,131,090 A 10/2000 Basso, Jr. et al.
6,202,923 B1 * 3/2001 Boyer et al. 235/375
6,315,720 B1 11/2001 Williams et al.

FOREIGN PATENT DOCUMENTS

WO WO 98/13783 4/1998
WO WO 99/10829 3/1999
WO WO 00/51053 8/2000

* cited by examiner

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

34 Claims, No Drawings

**METHODS FOR DELIVERING A DRUG TO A
PATIENT WHILE RESTRICTING ACCESS
TO THE DRUG BY PATIENTS FOR WHOM
THE DRUG MAY BE CONTRAINDICATED**

**CROSS-REFERENCE TO RELATED
APPLICATION**

This application is a continuation of U.S. application Ser. No. 09/694,217, filed Oct. 23, 2000 U.S. Pat. No. 6,315,720.

FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to foetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

- a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
- b. defining a set of information to be obtained from the patient, which information is probative of the risk that

such adverse side effect is likely to occur if the drug is taken by the patient;

- c. in response to the information set, assigning the patient to at least one of the risk groups; and
- d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term “drug,” as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term “side effect” refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term “likely to arise” means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term “prescriber” refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information,

educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

- 5 The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term “contraindicated” refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered “contraindicated,” as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

- 10 The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term “substantially,” as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

- 15 The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registra-

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tion card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer

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readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the

drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the

patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided

verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on fetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenicity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are

capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will

be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed

consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing.

Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacies who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved.

Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuberculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for

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the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of

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spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence

amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bio-availability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated

without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed is:

1. A method for delivering a drug to patients in need of the drug while restricting access to the drug by patients for whom the drug may be contraindicated, said method comprising permitting prescriptions for the drug to be filled by a pharmacy only after the pharmacy has retrieved an approval code for the prescription from a computer readable storage medium, wherein generation of the prescription approval code comprises the following steps:

- a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
- b. defining a set of information to be obtained from a patient, which information is probative of the risk that an adverse side effect is likely to occur if the drug is taken by the patient;
- c. in response to the information set, assigning the patient to at least one of the risk groups and entering the patient, the information and the patient's risk group assignment in the medium;
- d. based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and
- e. upon a determination that the risk is acceptable, generating the prescription approval code to be retrieved by the pharmacy before the prescription is filled.

2. A method according to claim 1 further comprising registering in the medium the physician who prescribed the drug.

3. A method according to claim 1 further comprising registering the pharmacy in the medium.

4. The method of claim 1 further comprising counseling the patient as to the risks of taking the drug and advising the patient as to risk avoidance measures, in response to the risk group assignment.

5. The method of claim 4 wherein the counseling comprises full disclosure of the risks.

6. The method of claim 5 wherein the prescription is filled only following the full disclosure and informed consent of the patient.

7. The method of claim 6 wherein the informed consent is registered in the computer readable storage medium prior to generation of the prescription approval code.

8. The method of claim 7 wherein the risk group assignment and the informed consent is transmitted to the computer readable storage medium by facsimile and interpreted by optical character recognition software.

9. The method of claim 1 wherein the set of information includes the results of diagnostic testing.

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10. The method of claim 9 wherein the diagnostic testing comprises genetic testing.
11. The method of claim 9 wherein the diagnostic testing is probative of the onset of the adverse side effect.
12. The method of claim 9 wherein the diagnostic testing is probative of the presence of a condition or disease for which the drug is contraindicated.
13. The method of claim 1 wherein the side effect is likely to arise in the patient.
14. The method of claim 1 wherein the side effect is likely to arise in a foetus carried by the patient.
15. The method of claim 1 wherein the side effect is likely to arise in a recipient or a foetus carried by a recipient of the bodily fluid of the patient.
16. The method of claim 15 wherein the recipient is a sexual partner of the patient.
17. The method of claim 1 further comprising:
- f. defining for each risk group a second set of information to be collected from the patient at periodic intervals;
 - g. obtaining the second set of information from the patient; and
 - h. entering the second set of information in the medium.
18. The method of claim 17 wherein the second set of information comprises a survey regarding the patient's behavior and compliance with the risk avoidance measures.
19. The method of claim 18 wherein the survey is conducted telephonically using an integrated voice response system.
20. The method of claim 17 wherein the patient is a female of childbearing potential and the second set of information comprises the results of a pregnancy test.
21. The method of claim 18 wherein the periodic interval comprises about 28 days.

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22. The method of claim 1 further comprising providing the patient with a contraceptive device or formulation.
23. The method of claim 1 wherein the adverse side effect comprises a teratogenic effect.
24. The method of claim 23 wherein the drug is thalido-mide.
25. The method of claim 23 wherein the teratogenic effect is likely to arise in a foetus carried by the patient.
26. The method of claim 23 wherein the teratogenic effect is likely to arise in a foetus carried by a recipient of the bodily fluid of the patient.
27. The method of claim 26 wherein the recipient of the bodily fluid of the patient is a sexual partner of the patient.
28. The method of claim 23 wherein the set of information includes the results of a pregnancy test.
29. The method of claim 28 wherein the prescription is filled for no more than about 28 days.
30. The method of claim 1 wherein the adverse side effect is likely to arise in patients who take the drug in combination with at least one other drug.
31. The method of claim 30 wherein the set of information is also probative of the likelihood that the patient may take the drug and the other drug in combination.
32. The method of claim 30 wherein the set of information includes the results of diagnostic testing.
33. The method of claim 32 wherein the diagnostic testing comprises testing for evidence of the use of the other drug.
34. The method of claim 32 wherein the diagnostic testing comprises testing for evidence which is indicative of the onset of the adverse side effect.

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EXHIBIT C



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(12) **United States Patent**
Williams et al.

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(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**

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This patent is subject to a terminal disclaimer.

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(63) Continuation of application No. 09/965,155, filed on Sep. 27, 2001, now Pat. No. 6,561,977, which is a continuation of application No. 09/694,217, filed on Oct. 23, 2000, now Pat. No. 6,315,720.

(51) **Int. Cl.**⁷ **A61B 5/00**

(52) **U.S. Cl.** **600/300; 128/920**

(58) **Field of Search** 600/301, 300, 600/304; 395/200-210; 128/920, 925, 904, 897; 707/102; 706/23; 705/2-4; 235/375

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,299,121 A 3/1994 Brill et al. 600/301

5,594,637 A 1/1997 Eisenberg et al. 600/300
5,619,991 A 4/1997 Sloane 600/300
5,660,176 A 8/1997 Iliff 600/300
5,845,255 A 12/1998 Mayaud 705/3
5,974,203 A 10/1999 Tadokoro et al. 382/309
6,014,631 A 1/2000 Teagarden et al. 705/3
6,045,501 A * 4/2000 Elsayed et al. 600/300
6,055,507 A 4/2000 Cunningham 705/3
6,063,026 A * 5/2000 Schauss et al. 600/300
6,128,620 A 10/2000 Pissanos et al. 707/102
6,131,090 A 10/2000 Basso, Jr. et al. 706/23
6,202,923 B1 * 3/2001 Boyer et al. 235/375
6,315,720 B1 11/2001 Williams et al. 600/300

FOREIGN PATENT DOCUMENTS

WO WO 98/13783 4/1998
WO WO 99/10829 3/1999
WO WO 00/51053 8/2000

* cited by examiner

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

34 Claims, No Drawings

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METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of patent application Ser. No. 09/965,155, filed Sep. 27, 2001, now U.S. Pat. No. 6,561,977, which is a continuation of patent application Ser. No. 09/694,217, filed Oct. 23, 2000, now U.S. Pat. No. 6,315,720, the entirety of each of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community

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anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to fetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to

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receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

- a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
- b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;
- c. in response to the information set, assigning the patient to at least one of the risk groups; and
- d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dis-

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persing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a

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registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the

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pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise

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female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where

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sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the

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patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on fetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth

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control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenicity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug.

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Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at

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least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of childbearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

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In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacies who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the

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prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuberculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

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The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient

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will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

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The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bio-availability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a

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rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

1. A method for delivering a drug to patients in need of the drug while restricting access to the drug by patients for whom the drug may be contraindicated, said method comprising permitting prescriptions for the drug to be filled by a pharmacy only after the pharmacy has received an approval code for the prescription from a computer readable storage medium, wherein generation of the prescription approval code comprises the following steps:

- a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
- b. defining a set of information to be obtained from the patient, which information is probative of the risk that an adverse side effect is likely to occur if the drug is taken by the patient;
- c. in response to the information set, assigning the patient to at least one of the risk groups and entering the patient, the information and the patient's risk group assignment into the medium;
- d. based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and
- e. upon a determination that the risk is acceptable, generating the prescription approval code to be received by the pharmacy before the prescription is filled.

2. A method according to claim 1 further comprising registering in the medium the physician who prescribed the drug.

3. A method according to claim 1 further comprising registering the pharmacy in the medium.

4. The method of claim 1 further comprising counseling the patient as to the risks of taking the drug and advising the patient as to risk avoidance measures, in response to the risk group assignment.

5. The method of claim 4 wherein the counseling comprises full disclosure of the risks.

6. The method of claim 5 wherein the prescription is filled only following the full disclosure and informed consent of the patient.

7. The method of claim 6 wherein the informed consent is registered in the computer readable storage medium prior to generation of the prescription approval code.

8. The method of claim 7 wherein the risk group assignment and the informed consent is transmitted to the com-

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puter readable storage medium by facsimile and interpreted by optical character recognition software.

9. The method of claim 1 wherein the set of information comprises the results of diagnostic testing.

10. The method of claim 9 wherein the diagnostic testing comprises genetic testing.

11. The method of claim 9 wherein the diagnostic testing is probative of the onset of the adverse side effect.

12. The method of claim 9 wherein the diagnostic testing is probative of the presence of a condition or disease for which the drug is contraindicated.

13. The method of claim 1 wherein the side effect is likely to arise in the patient.

14. The method of claim 1 wherein the side effect is likely to arise in a foetus carried by the patient.

15. The method of claim 1 wherein the side effect is likely to arise in a recipient or a foetus carried by a recipient of the bodily fluid of the patient.

16. The method of claim 15 wherein the recipient is a sexual partner of the patient.

17. The method of claim 1 further comprising:

f. defining for each risk group a second set of information to be collected from the patient at periodic intervals;

g. obtaining the second set of information from the patient; and

h. entering the second set of information in the medium.

18. The method of claim 17 wherein the second set of information comprises a survey regarding the patient's behavior and compliance with the risk avoidance measures.

19. The method of claim 18 wherein the survey is conducted telephonically using an integrated voice response system.

20. The method of claim 17 wherein the patient is a female of childbearing potential and the second set of information comprises the results of a pregnancy test.

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21. The method of claim 18 wherein the periodic interval comprises about 28 days.

22. The method of claim 1 further comprising providing the patient with a contraceptive device or formulation.

23. The method of claim 1 wherein the adverse side effect comprises a teratogenic effect.

24. The method of claim 23 wherein the drug is thalidomide.

25. The method of claim 23 wherein the teratogenic effect is likely to arise in a foetus carried by the patient.

26. The method of claim 23 wherein the teratogenic effect is likely to arise in a foetus carried by a recipient of the bodily fluid of the patient.

27. The method of claim 26 wherein the recipient of the bodily fluid of the patient is a sexual partner of the patient.

28. The method of claim 26 wherein the set of information includes the results of a pregnancy test.

29. The method of claim 28 wherein the prescription is filled for more than about 28 days.

30. The method of claim 1 wherein the adverse side effect is likely to arise in patients who take the drug in combination with at least one other drug.

31. The method of claim 30 wherein the set of information is also probative of the likelihood that the patient may take the drug and the other drug in combination.

32. The method of claim 30 wherein the set of information includes the results of diagnostic testing.

33. The method of claim 32 wherein the diagnostic testing comprises testing for evidence of the use of the other drug.

34. The method of claim 32 wherein the diagnostic testing comprises testing for evidence which is indicative of the onset of the adverse side effect.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,755,784 B2
DATED : June 29, 2004
INVENTOR(S) : Bruce A. Williams and Joseph A. Kaminski

Page 1 of 1

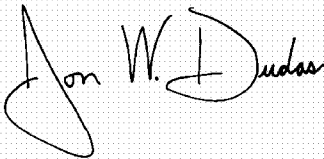
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 20,

Line 20, cancel the text "filled for more than about 28 days." and insert -- filled for no more than about 28 days. --.

Signed and Sealed this

Third Day of May, 2005

A handwritten signature in black ink on a light gray dotted background. The signature is written in a cursive style and appears to read "Jon W. Dudas".

JON W. DUDAS

Director of the United States Patent and Trademark Office

EXHIBIT D

US008315886B2

(12) **United States Patent**
Williams et al.(10) **Patent No.:** **US 8,315,886 B2**
(45) **Date of Patent:** ***Nov. 20, 2012**(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**(75) Inventors: **Bruce A. Williams**, Flemington, NJ (US); **Joseph K. Kaminski**, Hampton, NJ (US)(73) Assignee: **Celgene Corporation**, Warren, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 155 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/966,261**(22) Filed: **Dec. 13, 2010**(65) **Prior Publication Data**

US 2011/0082707 A1 Apr. 7, 2011

Related U.S. Application Data

(63) Continuation of application No. 11/437,551, filed on May 19, 2006, now Pat. No. 7,959,566, which is a continuation of application No. 11/028,144, filed on Jan. 3, 2005, now Pat. No. 7,141,018, which is a continuation of application No. 10/762,880, filed on Jan. 22, 2004, now Pat. No. 6,869,399, which is a continuation of application No. 10/383,275, filed on Mar. 7, 2003, now Pat. No. 6,755,784, which is a continuation of application No. 09/965,155, filed on Sep. 27, 2001, now Pat. No. 6,561,977, which is a continuation of application No. 09/694,217, filed on Oct. 23, 2000, now Pat. No. 6,315,720.

(51) **Int. Cl.**
G06Q 50/00 (2006.01)(52) **U.S. Cl.** **705/2**(58) **Field of Classification Search** **705/2**
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

5,299,121 A	3/1994	Brill et al.
5,594,637 A	1/1997	Eisenberg et al.
5,619,991 A	4/1997	Sloane
5,660,176 A	8/1997	Iliff
5,758,095 A	5/1998	Albaum et al.
5,832,449 A	11/1998	Cunningham
5,845,255 A	12/1998	Mayaud
5,974,203 A	10/1999	Tadokoro et al.
6,014,631 A	1/2000	Teagarden et al.
6,045,501 A	4/2000	Elsayed et al.
6,055,507 A	4/2000	Cunningham
6,063,026 A	5/2000	Schauss et al.
6,128,620 A	10/2000	Pissanos et al.
6,131,090 A	10/2000	Basso, Jr. et al.
6,202,923 B1	3/2001	Boyer et al.
6,315,720 B1	11/2001	Williams et al.
6,561,976 B2	5/2003	Elsayed et al.
6,561,977 B2	5/2003	Williams et al.
6,755,784 B2	6/2004	Williams et al.
6,767,326 B2	7/2004	Elsayed et al.

6,869,399 B2	3/2005	Williams et al.
6,908,432 B2	6/2005	Elsayed et al.
7,141,018 B2	11/2006	Williams et al.
7,959,566 B2	6/2011	Williams et al.
2005/0090425 A1	4/2005	Reardan et al.
2005/0216309 A1	9/2005	Reardan et al.
2005/0222874 A1	10/2005	Reardan et al.
2006/0129433 A1	6/2006	Koneru

FOREIGN PATENT DOCUMENTS

CA	2352619	1/2003
WO	WO 98/13783	4/1998
WO	WO 98/58338	12/1998
WO	WO 99/10829	3/1999
WO	WO 00/51053	8/2000
WO	WO 02/35440	5/2002

OTHER PUBLICATIONS"About the CNR", <https://www.clozarilcare.com/care/newUsr-RegPersonal.jsp>, 1 page.

"Complaint", In the United States District Court District of New Jersey, Case No. 2:07-cv-00286-PGS-RJH, Filed Jan. 18, 2007, 16 pages.

"Defendant Barr Laboratories Inc.'s Answer, Counterclaims and Demand for Jury Trial", In the United States District Court District of New Jersey, Case No. 2:07-cv-00286-PGS-RJH, filed Mar. 1, 2007, 67 pages.

"Guide to the Clozaril Patient Monitoring Service", A Reference Manual for the Clozaril Patient Monitoring Service, First Edition, Nov. 1997, 45 pages.

"Managing a Product under Attack: A Firsthand report on Colzaril", Medical Marketing & Media, Sep. 20, 1991, 26(10), 8 pages.

"Thalomid Information from Drugs.com", Jun. 22, 2006, accessed Feb. 1, 2008, <http://www.drugs.com/thalomid.html>.

Bakken et al., "Local Monitoring Center for Clozapine Therapy: Quality Assurance of Drug Treatment in a Group of Psychiatric Patients", Tidsskr Nor Laegeforen nr., 1998, 118, 1076-1078.

Bastani et al., "Development of the Clozaril Patient Management System", Psychopharmacology, 1998, 99, S122-S125.

Bates et al., "Effect of Computerized Physician order Entry and a Intervention on Prevention of Serious Medication Errors", The Journal of the American Medical Association, Oct. 21, 1998, 280(15), 1289-1316.

Behm, No Title, Am. Pharmacy 13th APhA Annual Meeting Highlights, 1990, NS30(6), p. 7.

Bender, "FDA approves reduced clozapine monitoring; increased patient access versus increased risk," Psychiatric Times, 1998, vol. XV, Issue 5, p. 13.

Black et al., "A centralized system for monitoring clozapine use in British Columbia," Psychiatric Services, 1996, 47(1), 81-83.

Bruera et al., "The uses of psychotropics in symptom management in advanced cancer," Psycho-Oncology., 1998, 7, 346-358.

(Continued)

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(74) Attorney, Agent, or Firm — Woodcock Washburn, LLP

(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

7 Claims, No Drawings

US 8,315,886 B2

Page 2

OTHER PUBLICATIONS

- Celgene Corporation, "Thalomid (thalidomide): Balancing the Benefits and the Risks", System for Thalidomide Education and Prescribing Safety, Nov. 1998, 52 pages.
- Celgene Corporation, "Thalomid (thalidomide): Clinical Information and Prescribing Guidelines", Reference Guide, Sep. 1998, 26 pages.
- Center for Drug Evaluation and Research Food and Drug Administration, "Forty-Seventh Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee", Sep. 4-5, 1997, 447 pages.
- Clark et al., "Thalidomide Capsules, A review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing," *Drug Safety*, 2001, 24(2), 87-117.
- Dimopoulos et al. "Adverse effects of Thalidomide administration in patients with neoplastic diseases," *Am. J. Med.*, Oct. 1, 2004, 117, 508-515.
- Dunning, "Hoechst Arava Pregnancy Registry Recommended to Track Teratogenicity", *The Pink Sheet*, Aug. 17, 1998, 60(033), 3 pages.
- Dunning, "Thalidomide Protocols and Patient Materials designed by FDA for Studies without Commercial Sponsors", *The Pink Sheet*, Nov. 18, 1996, 58(047), p. T&G-4.
- Fax to Ian Hilley of GenPharm Inc. to John Jackson of Celgene Corp., Oct. 14, 2004, re: Isotretinoin Pregnancy Risk Management Program, 26 pages.
- Freeman et al., "Will routine therapeutic drug monitoring have a place in clozapine therapy?," *Clinical Pharmacokinetics*, 1997, 32(2), 93-100.
- Honigfeld, "Effects of the Clozapine National Registry System on Incidence of Deaths related to Agranulocytosis", *Psychiatric Services*, Jan. 1996, 47(1), 52-56.
- Honigfeld, "Reducing clozapine-related morbidity and mortality: 5 years of experience with the clozaril national registry," *J. Clin. Psychiatry*, 1998, 59(Suppl. 3), 3-7.
- Janet Woodcock, "Supervisory Review of NDA 20-785", Center for Drug Evaluation and Research, Jul. 7, 1998, 12 pages.
- Kumar "Clozaril monitoring systems, registry data and analyses," Presentation, Novartis, 2002, 44 pages.
- Lieberman et al., "A report of clozapine-induced agranulocytosis in the United States (Incidence and risk factors)," *Drug Safety, Proceedings of a symposium held in London, 1991*, Hoffbrand, A.V, et al. (Eds.), 1-2.
- Love et al., "Computerized relational database for monitoring clozapine therapy," *Am. J. Hosp. Pharm.*, 1993, 1657-1662.
- Martin, "APhA says plan continues to interfere with pharmacists' practice prerogatives," *Am. Pharmacy*, 1991, NS31(5), 30-31.
- McCullough, "Roche Announces FDA Approval of Enhanced Pregnancy Prevention Program for Accutane", *Current News Releases*, Oct. 31, 2001, 1 page.
- Mitchell et al., "A Pregnancy-Prevention Program in Women of Childbearing Age Receiving Isotretinoin", *New England Journal of Medicine*, Jul. 13, 1995, 333(2), 101-106.
- Mordue, "Rational approach to clozaril distribution," *Am. Pharmacy*, 1990, NS30(6), p. 7.
- National Institutes of Health et al, "Thalidomide: Potential Benefits and Risks", Open Public Scientific Workshop, NIH Testimony, <http://www.fda.gov/oashi/patrep/nih99.html>, Sep. 9, 1997.
- National Institutes of Health et al, "Thalidomide: Potential Benefits and Risks", Open Public Scientific Workshop, NIH Testimony, <http://www.fda.gov/oashi/patrep/nih910.html>, Sep. 10, 1997.
- National Institutes of Health et al., "Thalidomide: Potential Benefits and Risks:", Open Public Scientific Workshop, Program and Abstracts, Sep. 9-10, 1997.
- Notification Letter dated Dec. 5, 2006 from Sterne Kessler to Celgene Corporation Re: Notification Pursuant to section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act.
- Notification Letter dated Dec. 15, 2006 from Sterne Kessler to Celgene Corporation Re: Supplemental Notification Pursuant to section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act.
- Notification Letter dated Dec. 19, 2006 from Sterne Kessler to Celgene Corporation Re: Supplemental Notification Pursuant to section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act.
- Notification Letter dated Oct. 4, 2007 from Barr Laboratories to Celgene Corporation Re: Supplemental Notification Pursuant to section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act.
- Oyesanmi et al., "Hematologic side effects of psychotropics," *Psychosomatics*, 1999, 40, 414-421.
- Pastuszak et al., "Use of the Retinoid Pregnancy Prevention Program in Canada: Patterns of Contraception Use in Women treated with Isotretinoin and Etretinate", *Reproductive Toxicology*, 1994, 8(1), 63-68.
- Patt et al., "Durable Clinical response of refractory hepatocellular to orally administered thalidomide," *Am. J. Clin. Oncol. (CCT.)*, 2000, 23(3), 319-321.
- Peck et al., "FDA's position on the clozaril patient management system," *Hospital & Community Psychiatry*, 1990, 41(8), 876-877.
- Richardson et al., "Thalidomide: Emerging role in cancer medicine," *Annu. Rev. Med.*, 2002, 53, 629-657.
- Richardson et al., "Thalidomide: The revival of a drug with Therapeutic promise in the treatment of cancer", In: *Cancer: Principles and Practice of Oncology*, 6th Ed., DeVita VT, Hellman S, Rosenberg SA, editors. Lippincott, Williams, and Wilkins, Philadelphia PA, 2001, 1-18.
- Roche Pharmaceuticals et al., "Isotretinoin Makers Reach Agreement with Celgene on S.T.E.P.S.® Risk Management Patents", Press Release, Nov. 23, 2004, 3 pages.
- Roche Pharmaceuticals et al., "Product Information", Physician's Desk Reference, 1997, 2252-2254 & 2377-2380.
- Roche, "Pregnancy Prevention Program for Women on Accutane Isotretinoin. Accutane Therapy for Woman of Childbearing Potential", Physicians' and Healthcare Professionals' Guide, 1994, 15 pages.
- Singhal et al. "Peer Viewpoint," *J. Supportive Oncology*, 1(3), Sep./Oct. 2003, 200-201.
- Sittig et al., "Computer-based Physician Order Entry: The State of the Art", *Journal of the American Medical Informatics Association*, Mar./Apr. Aug. 29, 1994, 1(2), 108-123.
- Somers, "Pharmacological Properties of Thalidomide (α -Phalidimido Glutarimide) a New Sedative-Hypnotic Drug," *Brit. J. Pharmacol.*, 1960, 15, 111-116.
- Teo et al., "Clinical pharmacokinetics of thalidomide," *Clin Pharmacokinetics*, Apr. 2004, 43(5), 311-327.
- Thomas et al., "Thalidomide Nursing Roundtable Update," American Academy of CME, Inc. and OmegaMed Inc., publishers., Sep. 2002.
- Trussell, "Contraceptive Efficacy", *Arch. Dermatol.*, Sep. 1995, 131, 1064-1068.
- Uhl et al., "Thalidomide Use in the US: Experience with Pregnancy Testing in the S.T.E.P.S.® Programme", *Drug Safety*, 2006, 29(4), 321-329.
- Villahermosa et al., "A Randomized, Double-Blind, Double-Dummy, Controlled Dose Comparison of Thalidomide for Treatment of Erythema Nodosum Leprosum", *Am. J. Trop. Med. Hyg.*, 2005, 72(5), 518-526.
- Webster, "Preventing Birth Defects due to Thalidomide Exposure", Sheraton Colony Square Hotel, Mar. 26, 1997, 27 pages.
- Zeldis et al., "A Comprehensive Program for Controlling and Monitoring Access to Thalidomide", *Frontiers in Fetal Health: A Global Perspective*, Aug. 1999, 1(2), 10-16.

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METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is continuation of U.S. application Ser. No. 11/437,551, filed May 19, 2006, which is a continuation of U.S. application Ser. No. 11/028,144, filed Jan. 3, 2005, now U.S. Pat. No. 7,141,018, which is a continuation of U.S. application Ser. No. 10/762,880, filed Jan. 22, 2004, now U.S. Pat. No. 6,869,399, which is a continuation of U.S. application Ser. No. 10/383,275, filed Mar. 7, 2003, now U.S. Pat. No. 6,755,784, which is a continuation of U.S. application Ser. No. 09/965,155, filed Sep. 27, 2001, now U.S. Pat. No. 6,561,977, which is a continuation of U.S. application Ser. No. 09/694,217, filed Oct. 23, 2000, now U.S. Pat. No. 6,315,720, the entirety of each of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and

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aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to fetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which

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prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

- a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
- b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;
- c. in response to the information set, assigning the patient to at least one of the risk groups; and
- d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and

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pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the methods described herein including, for example, providing patient education and counseling, and the like, as described in

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detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like. The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage

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medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug, such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of

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child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be

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probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the prescriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the

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patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on fetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenicity, birth control, and the like is preferably given only to female patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with part-

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ners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an addi-

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tional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a foetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In

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preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of child-bearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing

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the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacies who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the

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present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuberculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate

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that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be counseled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of

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a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol. Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share

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similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment protocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

1. A method of treating a male patient having a disease or condition responsive to a teratogenic drug comprising permitting prescriptions for the drug to be filled by a pharmacy only after the pharmacy has retrieved an approval code for the prescription, wherein the generation of the prescription approval code comprises the following steps:

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- (a) via a computer readable storage medium, registering a prescriber and the pharmacy with a distributor of a teratogenic drug;
- (b) determining whether the patient is able to understand and carry out instructions;
- (c) upon determination that the patient is able to carry out the instructions, providing verbal and written warnings of the hazard of taking the drug and exposing fetus to the drug;
- (d) further providing verbal and written warnings of the risk of possible contraception failure and of the need to use barrier contraception when having sexual intercourse with women of child bearing potential;
- (e) obtaining acknowledgement of said warnings from the patient;
- (f) via a computer readable storage medium, registering the patient with the distributor; and
- (g) upon obtaining the acknowledgement and registrations, generating via a computer readable storage medium the prescription approval code to be retrieved by the pharmacy before the prescription is filled; and
- (h) upon retrieving a prescription approval code, administering the drug to the patient.

2. The method of claim 1, wherein the acknowledgement requires the patient's acknowledgement of one or more of the following:

- (a) the understanding that the drug must not be taken if unprotected sex cannot be avoided;
- (b) the understanding of potential birth defects;
- (c) that the patient has been advised of the need for barrier contraception by the prescriber;
- (d) the obligation to inform the prescriber if the patient's sexual partner is suspected of becoming or being pregnant;
- (e) that the drug is solely for the use of the patient himself and must not be shared with any other person;
- (f) that the patient has read the information brochure or viewed the information film on the drug;
- (g) that the semen or blood must not be donated during the drug treatment;
- (h) that all of the patient's inquiries regarding the drug treatment have been answered by the prescribing physician; or
- (i) the patient's understanding that participation in a survey and patient registry is required during the drug treatment.

3. The method of claim 1 further comprising providing the patient, prior to generation of the approval code, with warnings of the side effects associated with administration of the drug, wherein said side effects are non-teratogenic side effects.

4. The method of claim 1 further comprising obtaining a written authorization by the prescriber prior to generation of the approval code.

5. The method of claim 1, wherein the prescription approval code is retrieved from a computer readable storage medium.

6. The method of claim 1, wherein the acknowledgement is a written informed consent.

7. The method of claim 6, wherein the written informed consent is registered in the medium prior to generation of the prescription approval code.

* * * * *

EXHIBIT E

US008626531B2

(12) **United States Patent**
Williams et al.(10) **Patent No.:** **US 8,626,531 B2**
(45) **Date of Patent:** ***Jan. 7, 2014**(54) **METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED**(75) Inventors: **Bruce A. Williams**, Flemington, NJ (US); **Joseph K. Kaminski**, Hampton, NJ (US)(73) Assignee: **Celgene Corporation**, Summit, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/591,622**(22) Filed: **Aug. 22, 2012**(65) **Prior Publication Data**

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G06Q 50/00 (2012.01)(52) **U.S. Cl.**
USPC **705/2**(58) **Field of Classification Search**
USPC **705/2**
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

5,299,121	A	3/1994	Brill et al.
5,594,637	A	1/1997	Eisenberg et al.
5,619,991	A	4/1997	Sloane
5,660,176	A	8/1997	Iliff
5,758,095	A	5/1998	Albaum et al.
5,832,449	A	11/1998	Cunningham
5,845,255	A	12/1998	Mayaud
5,974,203	A	10/1999	Tadokoro et al.
6,014,631	A	1/2000	Teagarden et al.
6,045,501	A	4/2000	Elsayed et al.
6,055,507	A	4/2000	Cunningham
6,063,026	A	5/2000	Schauss et al.
6,128,620	A	10/2000	Pissanos et al.

6,131,090	A	10/2000	Basso, Jr. et al.
6,202,923	B1	3/2001	Bayer et al.
6,315,720	B1	11/2001	Williams et al.
6,561,976	B2	5/2003	Elsayed et al.
6,561,977	B2	5/2003	Williams et al.
6,755,784	B2	6/2004	Williams et al.
6,767,326	B2	7/2004	Elsayed et al.
6,869,399	B2	3/2005	Williams et al.
6,908,432	B2	6/2005	Elsayed et al.
7,141,018	B2	11/2006	Williams et al.
7,959,566	B2	6/2011	Williams et al.
2005/0090425	A1	4/2005	Reardan et al.
2005/0216309	A1	9/2005	Reardan et al.
2005/0222874	A1	10/2005	Reardan et al.
2006/0129433	A1	6/2006	Koneru

FOREIGN PATENT DOCUMENTS

CA	2352619	1/2003
WO	WO 98/13783	4/1998
WO	WO 98/58338	12/1998
WO	WO 99/10829	3/1999
WO	WO 00/51053	8/2000
WO	WO 02/35440	5/2002

OTHER PUBLICATIONS"About the CNR", <https://www.clozarilcare.com/care/newUsr-ReqPersonal.jsp>, 1989 1 page.

"Complaint", In the United States District Court District of New Jersey, Case No. 2:07-cv-00286-PGS-RJH, Filed Jan. 18, 2007, 16 pages.

"Defendant Barr Laboratories Inc.'s Answer, Counterclaims and Demand for Jury Trial", In the United States District Court District of New Jersey, Case No. 2:07-cv-00286-PGS-RJH, filed Mar. 1, 2007, 67 pages.

"Guide to the Clozaril Patient Monitoring Service", A Reference Manual for the Clozaril Patient Monitoring Service, First Edition, Nov. 1997, 45 pages.

"Managing a Product under Attack: A Firsthand report on Colzaril", Medical Marketing & Media, Sep. 20, 1991, 26(10), 8 pages.

"Thalomid Information from Drugs.com", Jun. 22, 2006, accessed Feb. 1, 2008, <http://www.drugs.com/thalomid.html>.

Bakken et al., "Local Monitoring Center for Clozapine Therapy: Quality Assurance of Drug Treatment in a Group of Psychiatric Patients", Tidsskr Nor Laegeforen nr., 1998, 118, 1076-1078.

Bastani et al., "Development of the Clozaril Patient Management System", Psychopharmacology, 1998, 99, S122-S125.

Bates et al., "Effect of Computerized Physician order Entry and a Intervention on Prevention of Serious Medication Errors", The Journal of the American Medical Association, Oct. 21, 1998, 280(15), 1289-1316.

Behm, No Title, Am. Pharmacy 13th APhA Annual Meeting Highlights, 1990, NS30(6), p. 7.

(Continued)

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(57) **ABSTRACT**

Methods for delivering a drug to a patients in need of the drug, while restricting access to the drug by patients for whom the drug may be contraindicated are disclosed. The methods are of the type in which prescriptions for the drug are filled by a pharmacy only after a computer readable storage medium has been consulted to retrieve a prescription approval code. Embodiments are provided wherein the patients are assigned to risk groups based upon the risk that taking the drug will lead to an adverse side effect, and certain additional information, such as periodic surveys and diagnostic tests probative of the ongoing risk of the side effect developing are obtained before prescriptions for the drug are approved.

40 Claims, No Drawings

US 8,626,531 B2

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(56)

References Cited

OTHER PUBLICATIONS

Bender, "FDA approves reduced clozapine monitoring; increased patient access versus increased risk," *Psychiatric Times*, 1998, vol. XV, Issue 5, p. 13.

Black et al., "A centralized system for monitoring clozapine use in British Columbia," *Psychiatric Services*, 1996, 47(1), 81-83.

Bruera et al., "The uses of psychotropics in symptom management in advanced cancer," *Psycho-Oncology*, 1998, 7, 346-358.

Celgene Corporation, "Thalomid (thalidomide): Balancing the Benefits and the Risks", System for Thalidomide Education and Prescribing Safety, Nov. 1998, 52 pages.

Celgene Corporation, "Thalomid (thalidomide): Clinical Information and Prescribing Guidelines", Reference Guide, Sep. 1998, 26 pages.

Center for Drug Evaluation and Research Food and Drug Administration, "Forty-Seventh Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee", Sep. 4-5, 1997, 447 pages.

Clark et al., "Thalidomide Capsules, A review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing," *Drug Safety*, 2001, 24(2), 87-117.

Dimopoulos et al. "Adverse effects of Thalidomide administration in patients with neoplastic diseases," *Am. J. Med.*, Oct. 1, 2004, 117, 508-515.

Dunning, "Hoechst Arava Pregnancy Registry Recommended to Track Teratogenicity", *The Pink Sheet*, Aug. 17, 1998, 60(033), 3 pages.

Dunning, "Thalidomide Protocols and Patient Materials designed by FDA for Studies without Commercial Sponsors", *The Pink Sheet*, Nov. 18, 1996, 58(047), p. T&G-4.

Fax to Ian Hilley of GenPharm Inc. to John Jackson of Celgene Corp., Oct. 14, 2004, re: Isotretinoin Pregnancy Risk Management Program, 26 pages.

Freeman et al., "Will routine therapeutic drug monitoring have a place in clozapine therapy?," *Clinical Pharmacokinetics*, 1997, 32(2), 93-100.

Honigfeld, "Effects of the Clozapine National Registry System on Incidence of Deaths related to Agranulocytosis", *Psychiatric Services*, Jan. 1996, 47(1), 52-56.

Honigfeld, "Reducing clozapine-related morbidity and mortality: 5 years of experience with the clozaril national registry," *J. Clin. Psychiatry*, 1998, 59(Suppl. 3), 3-7.

Janet Woodcock, "Supervisory Review of NDA 20-785", Center for Drug Evaluation and Research, Jul. 7, 1998, 12 pages.

Kumar "Clozaril monitoring systems, registry data and analyses," Presentation, Novartis, 2002, 44 pages.

Lieberman et al., "A report of clozapine—induced agranulocytosis in the United States (Incidence and risk factors)," *Drug Safety, Proceedings of a symposium held in London, 1991*, Hoffbrand, A.V, et al. (Eds.), 1-2.

Love et al., "Computerized relational database for monitoring clozapine therapy," *Am. J. Hosp. Pharm.*, 1993, 1657-1662.

Martin, "APhA says plan continues to interfere with pharmacists' practice prerogatives," *Am. Pharmacy*, 1991, NS31(5), 30-31.

McCullough, "Roche Announces FDA Approval of Enhanced Pregnancy Prevention Program for Accutane", *Current News Releases*, Oct. 31, 2001, 1 page.

Mitchell et al., "A Pregnancy-Prevention Program in Women of Childbearing Age Receiving Isotretinoin", *New England Journal of Medicine*, Jul. 13, 1995, 333(2), 101-106.

Mordue, "Rational approach to clozaril distribution," *Am. Pharmacy*, 1990, NS30(6), p. 7.

National Institutes of Health et al., "Thalidomide: Potential Benefits and Risks", Open Public Scientific Workshop, NIH Testimony, <http://www.fda.gov/oashi/patrep/nih99.html>, Sep. 9, 1997.

National Institutes of Health et al., "Thalidomide: Potential Benefits and Risks", Open Public Scientific Workshop, NIH Testimony, <http://www.fda.gov/oashi/patrep/nih910.html>, Sep. 10, 1997.

National Institutes of Health et al., "Thalidomide: Potential Benefits and Risks", Open Public Scientific Workshop, Program and Abstracts, Sep. 9-10, 1997.

Notification Letter dated Dec. 5, 2006 from Sterne Kessler to Celgene Corporation Re: Notification Pursuant to section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act.

Notification Letter dated Dec. 15, 2006 from Sterne Kessler to Celgene Corporation Re: Supplemental Notification Pursuant to section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act.

Notification Letter dated Dec. 19, 2006 from Sterne Kessler to Celgene Corporation Re: Supplemental Notification Pursuant to section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act.

Notification Letter dated Oct. 4, 2007 from Barr Laboratories to Celgene Corporation Re: Supplemental Notification Pursuant to section 505(j)(2)(B)(ii) of the Federal Food, Drug and Cosmetic Act.

Oyesanmi et al., "Hematologic side effects of psychotropics," *Psychosomatics*, 1999, 40, 414-421.

Pastuszak et al., "Use of the Retinoid Pregnancy Prevention Program in Canada: Patterns of Contraception Use in Women treated with Isotretinoin and Etretinate", *Reproductive Toxicology*, 1994, 8(1), 63-68.

Patt et al., "Durable Clinical response of refractory hepatocellular to orally administered thalidomide," *Am. J. Clin. Oncol. Cct.* 2000, 23(3), 319-321.

Peck et al., "FDA's position on the clozaril patient management system," *Hospital & Community Psychiatry*, 1990, 41(8), 876-877.

Richardson et al., "Thalidomide: Emerging role in cancer medicine," *Annu. Rev. Med.*, 2002, 53, 629-657.

Richardson et al., "Thalidomide: The revival of a drug with Therapeutic promise in the treatment of cancer", In: *Cancer: Principles and Practice of Oncology*, 6th Ed., DeVita VT, Hellman S, Rosenberg SA, editors. Lippincott, Williams, and Wilkins, Philadelphia PA, 2001, 1-18.

Roche Pharmaceuticals et al., "Isotretinoin Makers Reach Agreement with Celgene on S.T.E.P.S.® Risk Management Patents", *Press Release*, Nov. 23, 2004, 3 pages.

Roche Pharmaceuticals et al., "Product Information", *Physician's Desk Reference*, 1997, 2252-2254 & 2377-2380.

Roche, "Pregnancy Prevention Program for Women on Accutane Isotretinoin. Accutane Therapy for Woman of Childbearing Potential", *Physicians' and Healthcare Professionals' Guide*, 1994, 15 pages.

Singhal et al. "Peer Viewpoint," *J. Supportive Oncology*, 1(3), Sep./Oct. 2003, 200-201.

Sittig et al., "Computer-based Physician Order Entry: The State of the Art", *Journal of the American Medical Informatics Association*, Mar./Apr. Aug. 29, 1994, 1(2), 108-123.

Somers, "Pharmacological Properties of Thalidomide (α -Phalidimido Glutarimide) a New Sedative-Hypnotic Drug," *Brit. J. Pharmacol.*, 1960, 15, 111-116.

Teo et al., "Clinical pharmacokinetics of thalidomide," *Clin Pharmacokinetics*, Apr. 2004, 43(5), 311-327.

Thomas et al., "Thalidomide Nursing Roundtable Update," *American Academy of CME, Inc. and OmegaMed Inc., publishers.*, Sep. 2002.

Trussell, "Contraceptive Efficacy", *Arch. Dermatol.*, Sep. 1995, 131, 1064-1068.

Uhl et al., "Thalidomide Use in the US: Experience with Pregnancy Testing in the S.T.E.P.S. ® Programme", *Drug Safety*, 2006, 29(4), 321-329.

Villahermosa et al., "A Randomized, Double-Blind, Double-Dummy, Controlled Dose Comparison of Thalidomide for Treatment of Erythema Nodosum Leprosum", *Am. J. Trop. Med. Hyg.*, 2005, 72(5), 518-526.

Webster, "Preventing Birth Defects due to Thalidomide Exposure", *Sheraton Colony Square Hotel*, Mar. 26, 1997, 27 pages.

Zeldis et al., "A Comprehensive Program for Controlling and Monitoring Access to Thalidomide", *Frontiers in Fetal Health: A Global Perspective*, Aug. 1999, 1(2), 10-16.

"First Amended Complaint for Patent Infringement", In the United States District Court District of New Jersey, Case No: 2:10-cv-05197-SDW-MCA, filed Jan. 7, 2011, 22 pages.

"Answer, Affirmative Defenses and Counterclaims to Plaintiff's First Amended Complaint, and Demand for Jury Trial", In the United States District Court District of New Jersey, Case No. Case No. 2:10-cv-05197-SDW-MCA, filed Jan. 14, 2011, 128 pages.

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(56)

References Cited

OTHER PUBLICATIONS

“Second Amended Complaint for Patent Infringement”, In the United States District Court District of New Jersey, Case No. Case No. 2:10-cv-05197-SDW-MCA, filed Mar. 25, 2011, 24 pages.

“Answer, Affirmative Defenses and Counterclaims to Plaintiff’s Second Amended Complaint, and Demand for Jury Trial”, In the United States District Court District of New Jersey, Case No. Case No. 2:10-cv-05197-SDW-MCA, filed Apr. 15, 2011, 96 pages.

“Complaint for Patent Infringement”, In the United States District Court District of New Jersey, Case No. Case No. 2:10-cv-05197-SDW-MCA, filed Jul. 20, 2012, 238 pages.

“Complaint for Patent Infringement”, In the United States District Court District of New Jersey, Case No. Case No. 2:10-cv-05197-SDW-MCA, filed Oct. 8, 2010, 206 pages.

“Defendant NATCO Pharma Limited’s Answer, Affirmative Defenses, Counterclaims and Demand for Jury Trial”, In the United States District Court District of New Jersey, Case No. Case No. 2:10-cv-05197-SDW-MCA, filed Nov. 18, 2010, 122 pages.

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METHODS FOR DELIVERING A DRUG TO A PATIENT WHILE RESTRICTING ACCESS TO THE DRUG BY PATIENTS FOR WHOM THE DRUG MAY BE CONTRAINDICATED

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 12/966,261, filed Dec. 13, 2010, which is a continuation of U.S. application Ser. No. 11/437,551, filed May 19, 2006, now U.S. Pat. No. 7,959,566, which is a continuation of U.S. application Ser. No. 11/028,144, filed Jan. 3, 2005, now U.S. Pat. No. 7,141,018, which is a continuation of U.S. application Ser. No. 10/762,880, filed Jan. 22, 2004, now U.S. Pat. No. 6,869,399, which is a continuation of U.S. application Ser. No. 10/383,275, filed Mar. 7, 2003, now U.S. Pat. No. 6,755,784, which is a continuation of U.S. application Ser. No. 09/965,155, filed Sep. 27, 2001, now U.S. Pat. No. 6,561,977, which is a continuation of U.S. application Ser. No. 09/694,217, filed Oct. 23, 2000, now U.S. Pat. No. 6,315,720, the entirety of each of which is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to improved methods for delivering a drug to a patient. More particularly, the present invention relates to novel methods for delivering a teratogenic or other potentially hazardous drug to a patient in need of the drug, while avoiding the occurrence of known or suspected side effects of the drug. The novel methods permit the distribution to patients of drugs, particularly teratogenic drugs, in ways wherein such distribution can be carefully monitored and controlled.

BACKGROUND OF THE INVENTION

Many beneficial drugs are known or suspected of producing adverse side effects in certain individuals. These side effects may be manifest in the patient taking the drug, in a foetus (i.e. fetus) carried by the patient, or in a recipient (or foetus carried by a recipient) of the bodily fluids of the patient. In some cases, administration of the drug may be acceptable in some patients, but absolutely contraindicated in other patients. For example, drugs known or suspected of causing birth defects if taken by a pregnant woman (i.e. teratogenic drugs), may nonetheless be beneficial for treating certain conditions. However, because of the teratogenic properties of the drug, administration to pregnant women must be avoided. Other drugs are known which may be beneficially employed in the general population, but must be avoided by individuals having a certain preexisting condition, or those concurrently taking certain other medication(s), due to adverse side effects which may develop in those individuals.

One such drug which is known to produce adverse side effects, but which may nevertheless be beneficially employed in certain patients is thalidomide. Thalidomide is a drug which was first synthesized in Germany in 1957. Beginning in 1958, it was marketed in many countries for use as a sedative, although it was never approved for use in the United States. After reports of serious birth defects, thalidomide was withdrawn from all markets by 1962. However, during the years it was used, it was found to be effective in treating erythema nodosum leprosum (ENL), a condition of leprosy, and the U.S. Food and Drug Administration (FDA) has made the drug available for this specific use via a program of the Public

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Health Service. More recently, investigators have found that thalidomide may be effective in treating AIDS wasting and aphthous ulcers occurring in AIDS patients. In addition, treatments for other diseases, such as a number of neoplastic diseases including cancers, rheumatoid arthritis, and macular degeneration, are also believed to be possible. The FDA has recently approved an application by Celgene Corporation, which is the assignee of the present patent application, to market thalidomide for the treatment of ENL. The medical community anticipates that thalidomide will be used for treatment of additional conditions and diseases, including those set forth above. However, due to the severe teratogenic risk of thalidomide, methods are needed to control the distribution of this drug so as to preclude administration to fetuses.

In this regard, U.S. Pat. No. 6,045,501, to Elsayed et al., provides methods for delivering a drug to a patient while preventing the exposure of a foetus or other contraindicated individual to the drug. According to the methods of this patent, prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. Improvements to this method may be useful, however, to minimize and simplify the demands on the pharmacy, thereby improving compliance with the system of distribution, and reducing the risk that the drug will be dispensed to a contraindicated individual.

Methods for monitoring and educating patients to whom a drug is distributed have been developed in connection with Accutane (isotretinoin). Accutane, which is a known teratogen, is a uniquely effective drug for the treatment of severe, recalcitrant, nodular acne. A pregnancy prevention program was developed, and the Slone Epidemiology Unit of Boston University designed and implemented a survey to evaluate these efforts. The survey identified relatively low rates of pregnancy during Accutane treatment, which suggests that such a program can be effective. With more than about 325,000 women enrolled to date in the Accutane survey, it is also clear that such a large-scale study can be conducted. Enrollment in the Accutane survey is voluntary, however. Accordingly, assessing the representativeness of the women who have been enrolled in the survey has been problematic, and it has been difficult to determine whether the survey results can be generalized to all female Accutane users. Thus, an improved survey is needed which would be representative of all users of a particular drug, such as thalidomide, who obtain the drug through legal distribution channels. There are also no mechanisms provided to assure compliance with the program or to limit distribution of the drug to participants in the survey.

Because drug sharing may frequently occur among AIDS patients, which may result in placing a foetus at risk, a program is needed which can be used to educate men and women about the risk of teratogenic drugs, such as thalidomide. In addition, a system is needed for the controlled distribution of a drug, in which of all users of the drug, including prescribers, pharmacies, and patients, may be accountable for their compliance with methods that may be established to minimize the risk that a contraindicated individual will be exposed to the drug. The present invention is directed to these, as well as other important ends.

SUMMARY OF THE INVENTION

The present invention is directed to improved methods for delivering a drug to a patient in need of the drug, while

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avoiding the occurrence of an adverse side effect known or suspected of being caused by the drug, of the type in which prescriptions for the drug are filled only after a computer readable storage medium has been consulted to assure that the prescriber is registered in the medium and qualified to prescribe the drug, that the pharmacy is registered in the medium and qualified to fill the prescription for the drug, and the patient is registered in the medium and approved to receive the drug. In one embodiment of the invention, there are provided improved methods comprising the steps of:

- a. defining a plurality of patient risk groups based upon a predefined set of risk parameters for the drug;
- b. defining a set of information to be obtained from the patient, which information is probative of the risk that such adverse side effect is likely to occur if the drug is taken by the patient;
- c. in response to the information set, assigning the patient to at least one of the risk groups; and
- d. entering the risk group assignment in the medium before the patient is approved to receive the drug.

The improved methods described herein provide advantageous and effective means for monitoring, controlling and authorizing the distribution to patients of drugs known or suspected of causing adverse side effects. The methods of the present invention include a variety of checks and balances which serve to limit unauthorized and possibly inappropriate distribution of the drug. These methods are particularly applicable to distribution of teratogenic drugs, in which case the checks and balances may be particularly advantageous for preventing distribution of the drug to patients whose use of the drug may pose an unacceptable risk that a foetus carried by the patient or a recipient of the bodily fluids of the patient will be exposed to such drugs. Accordingly, the present methods may be advantageously used to avoid exposure of foetuses to teratogenic drugs, thereby avoiding the terrible birth defects which may result from such exposure.

The invention is not limited to the distribution of teratogenic drugs; other potentially hazardous drugs may also be distributed in accordance with embodiments of this invention and such drugs may be distributed in such a fashion that persons for whom such drugs are contraindicated will not receive them. These and other aspects of the invention will become more apparent from the present description and claims.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present invention is directed generally to methods for the delivery of drugs known or suspected of causing an adverse side effect, especially teratogenic drugs, to patients. The term "drug," as used herein, refers to any substance which is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure or function of the body. The term "side effect" refers to any abnormality, defect, mutation, lesion, degeneration or injury which may be caused by taking the drug. The side effect may be one which is likely to arise in the patient or in a foetus (i.e., fetus) carried by the patient. The side effect may also be one which is likely to arise in a recipient of the bodily fluid of the patient, or foetus carried by such recipient. The term "likely to arise" means that the side effect known or suspected of being caused by the drug may be expected to occur at a higher incidence rate in a particular individual or group of individuals.

Generally speaking, the methods of the present invention may be desirably and advantageously used to educate and

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reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug. As used herein, the term "prescriber" refers to any individual who is capable of prescribing drugs, including, for example, a medical doctor. Such education and reinforcement of actions and behavior are often necessary to ensure proper prescribing and dispensing of the drug, as well as patient compliance with taking the drug. A wide variety of educational materials may be employed to ensure proper prescribing, dispensing and patient compliance according to the methods described herein, including, for example, a variety of literature and other materials, such as, for example, product information, educational brochures, continuing education monographs, videotapes and the like which may describe the risks and benefits associated with taking the particular drug and measures which may be taken to avoid those risks.

The methods described herein may be advantageously employed to avoid delivery of one or more drugs known or suspected of causing an adverse side effect to a patient for whom the drugs may be contraindicated. As used herein, the term "contraindicated" refers to any condition in a patient which renders a particular line of treatment, including the administration of one or more drugs, undesirable or improper. This condition may be preexisting, or may develop while the patient is taking the drugs, including conditions which may result directly or indirectly from treatment with the drugs. Thus, contraindicated drugs include, for example, teratogenic drugs whose administration, for example, to pregnant patients is importantly avoided due to the risks to the foetus. Drugs may also be considered "contraindicated," as the term is used herein, if use of a drug by patients who are also taking another drug is known or suspected of producing an adverse side effect in those patients, or in a foetus carried by such patients.

The methods of the present invention are especially advantageously employed for the delivery to a patient of a teratogenic drug. The delivery of a teratogenic drug to a patient may be advantageously achieved with the present methods while substantially (including completely) avoiding the delivery of the drug to a foetus. The term "substantially," as used in reference to avoiding the delivery of a teratogenic drug to a foetus, generally means that there is an avoidance rate of delivering the drug to a foetus of greater than about 50%. Preferably, the avoidance rate is greater than about 55%, with an avoidance rate of greater than about 60% being more preferred. Even more preferably, the avoidance rate is greater than about 65%, with an avoidance rate of greater than about 70% being still more preferred. Yet more preferably, the avoidance rate is greater than about 75%, with an avoidance rate of greater than about 80% being still more preferred. In even more preferred embodiments, the avoidance rate is greater than about 85%, with an avoidance rate of greater than about 90% being yet more preferred. Still more preferably, the avoidance rate is greater than about 95%. In particularly preferred embodiments, a teratogenic drug may be delivered to patients with completely no delivery to foetuses (i.e., 100% avoidance rate).

The drug delivery methods of the present invention preferably involve, inter alia, registering in a computer readable storage medium prescribers who are qualified to prescribe the involved drug, including, for example, teratogenic drugs. Once registered in the computer readable storage medium, the prescriber may be eligible to prescribe the drug to patients in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the prescriber may be required to comply with various aspects of the

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methods described herein including, for example, providing patient education and counseling, and the like, as described in detail below. The registration of the prescriber in the computer readable storage medium may be achieved by providing the prescriber, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the prescriber is being registered to prescribe, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The prescriber will preferably complete the registration card or form by providing information requested therein, and the registration card or form will preferably be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration materials, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the prescriber in the registration card or form may include, for example, the prescriber's name, address, and affiliation, if any, with one or more health care institutions. The prescriber's information in the registration card or form is then entered into the computer readable storage medium. It is contemplated that the registration of the prescriber into the computer readable storage medium may also be achieved, for example, by telephone, and/or through the use of an integrated voice response system. Suitable computer readable storage media which may be employed for registration of the prescribers (as well as the pharmacies and patients, as discussed below) will be apparent to one of ordinary skill in the art, once armed with the teachings of the present application.

In accordance with the methods described herein, pharmacies who are qualified to fill prescriptions for the particular drug being prescribed including, for example, teratogenic drugs, are also preferably registered in a computer readable storage medium. The computer readable storage medium in which the pharmacies are registered may be the same as, or different from the computer readable storage medium in which the prescribers are registered. Once registered in the computer readable storage medium, the pharmacies may be eligible to dispense the involved drug to patients who are in need of the drug. Generally speaking, in order to become registered in the computer readable storage medium, the pharmacy may be required to comply with various aspects of the methods described herein including, for example, registering the patient (preferably also in a computer readable storage medium), ensuring that the patient complies with certain aspects of the drug delivery methods, as well as other aspects of the present methods, as described in detail below. As with the registration of the prescriber in the computer readable storage medium, the registration of the pharmacy may be achieved by providing the pharmacy, for example, by mail, facsimile transmission, or on-line transmission, with a registration card or form, preferably together with appropriate educational materials concerning, for example, the particular drug for which the pharmacy is being registered to dispense, as well as suitable methods for delivering the drug to the patient, including the drug delivery methods described herein. The pharmacy may then have the registration card or form completed by providing the information requested therein, which thereafter may be returned to the manufacturer or distributor of the drug, or other authorized recipient of the registration card or form, for example, by mail, facsimile transmission or on-line transmission. Information which may be requested of the pharmacy in the registration card or form may include, for example, the pharmacy's name, address, and affiliation, if any, with any health care institution such as, for example, a hospital, health care organization, and the like.

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The pharmacy's information in the registration card or form is then preferably entered into the computer readable storage medium. It is contemplated that the registration of the pharmacy into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

As noted above, the drug delivery methods described herein also preferably involve the registration of the patient in a computer readable storage medium. The computer readable storage medium in which the patients are registered may be the same as, or different from the computer readable storage medium in which the prescriber and/or pharmacy is registered. Generally speaking, in order to become registered in the computer readable storage medium, the patient may be required to comply with various aspects of the methods described herein. The registration of the patient may be carried out by the registered pharmacy, for example at the time of the patient's initial visit to the pharmacy. It has been found, however, that it may be more efficient, and better compliance with the methods of the present invention may be provided, if registration of the patient is carried out by the registered prescriber of the drug at the time the initial prescription is generated.

In preferred form, the prescriber will typically have a registration card or form filled out for the patient, which includes information on the patient, such as the patient's name, sex, mailing address, date of birth, and the like. Information on the prescribing prescriber and dispensing pharmacy, such as the information described above for the registration thereof, may also be desirably entered on the patient registration card or form. The completed card or form may then be forwarded to the manufacturer or distributor of the drug, or other authorized recipient of the registration form, for example, by mail, facsimile transmission or on-line transmission. Where registration is by mail or facsimile, entry of the registration into the computer readable storage medium may preferably include the use of optical character recognition (OCR) software. It is also possible that the registration of the patient into the computer readable storage medium may also be achieved, for example, by telephone and/or through the use of an integrated voice response system.

Preferably, information will also be collected from the patient that may be probative of the risk that a known or suspected side effect will occur if the drug is taken by the patient. This information may then be compared with a predefined set of risk parameters for the drug, which in turn define a plurality of risk groups, so that analysis of the information will permit assignment of the patient to at least one of the risk groups. Preferably, this risk group assignment is then also entered into the computer readable storage medium. This assignment may be performed by the prescriber, who may then include the risk group assignment on the patient's registration card or form, or may be performed by another individual, such as a nurse, technician, or office personnel, who preferably interprets the information and assigns the patient to one of the risk groups, accordingly.

As discussed above, it is preferable that a plurality of risk groups, each based upon a predefined set of risk parameters, be established for the drug which is to be administered. As will be evident to those of skill in the art, the risk parameters to be considered and the risk groups defined by those parameters, will be based upon factors which influence the risk that a known or suspected adverse side effect will occur if the patient receives the drug, and will vary depending upon the drug in question. Where the drug is a teratogenic drug, for example, such risk parameters may include elements which would impact the risk of a foetus being exposed to the drug,

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such as the age, sex and reproductive status of the patient. For example, a first risk group may comprise female patients of child bearing potential; a second risk group may comprise female patients of non-child bearing potential; a third risk group may comprise sexually active male patients; and a fourth risk group may comprise sexually inactive male patients. Additionally, there may be a risk group established for patients to whom administration of the drug may be strictly contraindicated, and patients assigned to such a group will not be approved to receive the drug. For other drugs, different factors, such as those influencing the likelihood that certain preexisting conditions may exist, or the likelihood of certain other drugs being used concomitantly with the prescribed drug, may define the relevant risk parameters.

By assigning each patient to a risk group, the steps that will be taken to minimize the chance that the drug is dispensed to a contraindicated patient, and to minimize the risk that a known or suspected adverse side effect will occur, can be tailored to suit the circumstances of that particular patient. For example, depending upon which risk group a patient is assigned to, additional information may be collected from the patient. As discussed more fully below, such additional information may be in the form, for example, of a patient survey. Such additional information may also include the results of certain diagnostic tests which have been performed. Based upon the additional information, the patient's risk group assignment may then remain the same, or the patient may be assigned to a different risk group, which may in turn require that further additional information be collected from the patient.

In accordance with the present invention, the monitoring of two, three or more drugs either administered to or proposed for administration to a patient may also be accomplished in order to avoid or diminish the likelihood of the occurrence of one or more side effects. Thus, combinations of drugs which, when administered to an individual patient, may give rise to an increased likelihood of side effects, may be registered in a computer readable storage medium, and the patient's risk group assignment may be reflective of this increased risk. A physician is registered to prescribe at least one of the drugs for a patient and a pharmacy is registered to fill such prescription. In this way, through assignment of such patient to one or more risk groups, the avoidance of harmful drug interactions may be attained.

It is preferred that for any given risk group, there may be defined a predetermined additional set of information which is to be collected from the patient. This additional set of information may be obtained prior to the initial dispensation of the drug to the patient and/or may be obtained from the patient on a periodic basis. This information may include information not previously obtained from the patient, or may simply reiterate previously asked questions, and repeat diagnostic tests which were conducted previously. The information may relate to the patient's conduct, or may relate to the patient's past or ongoing medical treatment, such as other procedures or medication which the patient may have received or is still receiving. For example, the additional set of information may be in the form of a survey or questionnaire regarding the patient's behavior and compliance with risk avoidance measures and may thus be probative of whether the risk of occurrence of an adverse side effect has increased, decreased or remained the same. Based upon the responses by the patient, the patient's risk group assignment may, if appropriate, be changed accordingly. Alternatively, where side effects which are known or suspected of being caused by a combination of drugs, the questions asked of the patient may be probative of the likelihood that the patient may take such a

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combination of drugs. Similarly, where sharing of drugs by the patient may be a matter of concern, the survey may be probative of the risk that the patient may be sharing the hazardous drug with another, and hence increase the risk that a contraindicated individual may receive the drug.

The additional information may also include the results of certain diagnostic tests which have been performed on the patient. Such diagnostic tests may be probative, for example, of the risk of exposure of a foetus to a teratogenic drug, may test for the presence of a risk factor for the adverse side effect of concern, or may be probative of the onset of that side effect. Where the use of combinations of more than one drug are known or suspected of causing an increased risk of the occurrence of a side effect, the diagnostic testing may include testing for the presence of one or more of those drugs, or evidence of the use by the patient of such other drugs. Additionally, diagnostic tests may be probative of the concentration of one or more drugs, including the prescribed drug or drugs, to assure that appropriate dosing is maintained.

Such diagnostic testing may be conducted on any bodily fluid or waste product of the patient, including the blood, serum, plasma, saliva, semen or urine, as well as the feces. Diagnostic testing may also be performed on a biopsy of any tissue of the patient or may include genetic testing, which may be indicative of a genetic predisposition to a particular adverse side effect. Other forms of diagnostic testing, such as diagnostic imaging, or tests which may be probative of the proper functioning of any tissue, organ or system are also contemplated. Preferably, the additional information and/or diagnostic test results are obtained and entered in the computer readable storage medium before the patient is approved to receive the drug. Additionally, where the information indicates that the risk of the adverse side effect occurring outweighs the potential benefit of the drug, the patient may be assigned to a risk group that will preclude approval of dispensation of the drug to that patient.

In accordance with the methods of the present invention, therefore, the delivery of the drug to the patient may involve the following steps. As a prelude to prescribing and dispensing the drug to the patient, the prescriber and the pharmacy are registered in one or more appropriate computer readable storage media, as described above. If the prescriber is not registered in the computer readable storage medium, the prescriber will be ineligible to prescribe the drug. Similarly, if the pharmacy is not registered in the computer readable storage medium, the pharmacy will be ineligible to dispense the drug.

In the course of an examination of a patient, including patients suffering from one or more diseases and/or disorders such as, for example, erythema nodosum leprosum (ENL), the prescriber may determine that the patient's condition would be improved by the administration of a drug such as, for example, a teratogenic drug, including thalidomide. Prior to prescribing the drug, the prescriber preferably counsels the patient, for example, on the various risks and benefits associated with the drug. For example, the prescriber preferably discusses the benefits associated with taking the drug, while also advising the patient on the various side effects associated therewith. In embodiments of the invention wherein the prescriber assigns the patient to a specific risk group, the disclosure is preferably tailored to that risk group assignment. Thus, a patient who may acquire or impart a condition or disease for which the drug is contraindicated is preferably counseled by the prescriber on the dangers associated therewith and advised as to risk avoidance measures which may be instituted. Preferably the patient is provided full disclosure of all the known and suspected risks associated with taking the drug. For example, in the case of teratogenic drugs, the pre-

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scriber preferably counsels the patient on the dangers of exposing a foetus, either one which may be carried by the patient or one carried by a recipient of the bodily fluids of the patient, to the teratogenic drug. Such counsel may be provided verbally, as well as in written form. In preferred embodiments, the prescriber provides the patient with literature materials on the drug for which a prescription is contemplated, such as product information, educational brochures, continuing education monographs, and the like. Thus, in the case of methods involving teratogenic drugs, the prescriber preferably provides patients with literature information, for example, in the form of the aforesaid product information, educational brochures, continuing education monographs, and the like, warning the patient of the effects of the drug on foetuses. In the case of other drugs which are known or suspected of causing an adverse side effect, the patient is counseled as to the dangers of taking the drugs, and of steps which may be taken to avoid those risks. For example, if the concomitant use of the drug and another drug, for example alcohol, is to be avoided, the prescriber advises the patient of the risks of drinking alcohol while taking the drug.

With particular reference to counseling provided in connection with teratogenic drugs, the prescriber preferably counsels female patients that such drugs must never be used by pregnant women. If the patient is a female of child-bearing potential (i.e., a woman who is capable of becoming pregnant), the prescriber preferably counsels the patient that even a single dosage of certain teratogenic drugs, such as thalidomide, may cause birth defects. Accordingly, the patient is preferably counseled to avoid sexual intercourse entirely, or if sexually active, to use appropriate forms of contraception or birth control. For both male and female patients, the prescriber preferably provides counsel on the importance of using at least two forms of effective birth control methods, with one form preferably being a highly effective hormonal method, and the other form preferably being an effective barrier method. The patients are preferably counseled to use the birth control methods for a period of time prior to and during treatment with the teratogenic drug, as well as for a period of time after treatment with the drug has been terminated. In preferred embodiments, the patient is counseled to use at least two forms of birth control for at least about 4 weeks prior to initiation of treatment, during treatment, and for at least about 4 weeks after treatment has been terminated. It may be desirable for the prescriber to personally provide female patients who are capable of becoming pregnant with one or more contraceptive devices or formulations.

Male patients who are being prescribed a teratogenic drug are preferably counseled to use condoms every time they engage in sexual relations, since many teratogenic drugs may be found in semen. Male patients are also preferably counseled to contact their prescriber if they have sexual intercourse without a condom, and/or if it is believed that they may have caused a pregnancy. As with female patients, it may be desirable for the prescriber to provide male patients who are capable of impregnating female patients with a contraceptive device or formulation. Other advice relative to birth control that the prescriber may provide to the patient would be apparent to one skilled in the art, once armed with the teachings of the present application. If the prescriber who is prescribing the teratogenic drug is unaware of certain aspects of the available forms of birth control and the advantages and disadvantages associated therewith, the patient should be referred to a prescriber who is knowledgeable on such matters, prior to being prescribed the involved drug. Generally speaking, as discussed below, counseling on teratogenicity, birth control, and the like is preferably given only to female

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patients who are capable of becoming pregnant, or to male patients who are capable of having sexual relations with partners who are or can become pregnant. In this manner, unnecessary counseling, for example, to women who are no longer of child-bearing age or men who are incapable of sexual relations with such women, may be avoided.

With further reference to methods involving teratogenic drugs, it is also preferred that the prescriber advise the patient to not share the drug with anyone else, and particularly that the drug should be kept out of the reach of children as well as women of child-bearing potential. In the case of female patients, particularly female patients of child-bearing potential, the prescriber should give the patient a pregnancy test, preferably a serum pregnancy test, prior to and during treatment with the teratogenic drug. To begin receiving the teratogenic drug and to continue taking the drug, female patients of child-bearing potential should continue to have negative pregnancy tests. The patient is also preferably counseled by the prescriber to discard or return to the prescriber, pharmacy, manufacturer or distributor any unused portion of the prescribed drug.

As would be apparent to one of ordinary skill in the art, once armed with the teachings of the present application, one or more aspects of the counseling described above may be applicable, in certain circumstances, for drugs other than teratogenic drugs.

In addition to receiving counseling on the drug being prescribed, including counseling, for example, on birth control, and prior to receiving a prescription for the drug, the methods of the present invention preferably involve requiring the patient to fill out an informed consent form which is signed by the prescriber, as well as the patient. The prescriber should retain a copy of the informed consent form for his/her records. Verification that the patient has given his/her informed consent may also be registered in the computer readable storage medium. Preferably, this verification is provided by the prescriber, and may be included, for example, with the patient registration information and risk group assignment. It has surprisingly been found that by having the prescriber, rather than the pharmacy, verify the patient's informed consent, the methods of the present invention may operate more efficiently, leading to better compliance, and hence decreased risk that the adverse side effect will occur, may be achieved.

By filling out and signing an informed consent form, the patient acknowledges that he/she understands the risks associated with taking the drug. In the informed consent form, the patient preferably agrees to comply with the risk avoidance measures provided, and to behave in a manner which is consistent with the prescriber's counsel. For example, in cases involving, for example, teratogenic drugs, the patient may agree to use at least one form of birth control, with female patients agreeing to use at least two forms of birth control. In preferred embodiments, where the patient's risk group assignment so dictates, the patient will agree to undergo periodic diagnostic testing relevant to the risk that the adverse side effect to be avoided may occur or be occurring. In preferred embodiments involving teratogenic drugs, female patients preferably agree also to undergo pregnancy testing, preferably serum pregnancy testing, before, during and after treatment with the teratogenic drug. Female patients preferably will also acknowledge that, at the time they are being prescribed the drug, especially teratogenic drugs, they are not pregnant, they will immediately stop taking the drug if they become pregnant, and they will not try to become pregnant for at least 4 weeks after treatment with the drug is terminated. Female patients, especially female patients for whom a teratogenic drug will be administered, preferably further agree

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to contact their prescriber if they wish to change one or more of the birth control methods being used and to have an additional pregnancy test if a menstrual period is missed. Female patients, especially female patients to be treated with teratogenic drugs, will preferably agree also to not breast-feed while being treated with the drug.

Male patients who are being prescribed the drugs according to the methods described herein, especially teratogenic drugs, will preferably agree to avoid having unprotected sexual relations with a woman, particularly a woman of child-bearing potential during treatment with the drug. In doing so, male patients will preferably further agree to use a condom during sexual relations with a woman, with latex condoms being preferred. Both male and female patients will also preferably agree to not share the drug with anyone, and to acknowledge that they cannot donate blood while taking the drug, with male patients agreeing also to not donate sperm while taking the drug. In addition, the patients will preferably agree to take part in a confidential patient survey, for example, before, during and after treatment with the drug. The patient survey provides information, for example, to the prescriber, manufacturer and/or distributor of the drug, as well as any group or body which may be established to generally provide oversight on the distribution of the drug, on information regarding the general lifestyle of the patient, including detailed information on the patient's sexual behavior. In this manner, the survey may assist in identifying patients who engage in risky behavior, as well as patients who are non-compliant with the methods described herein. Such risky behavior and/or non-compliance may lead to a suspension or intervention of the patient's treatment with the drug, with re-education being provided to the patient.

The information obtained from the survey is preferably also entered into the computer readable storage medium. Once entered into the computer readable storage medium, the prescriber, manufacturer and/or distributor of the drug may be able to glean therefrom information regarding the level of risk associated with the administration of the involved drug to the various patients. Accordingly, it may be possible to identify, from among the entire population of registered patients, one or more subpopulations of patients for which the involved drug may be more likely to be contraindicated. For example, it may be possible to identify a subpopulation of female patients who are capable of becoming pregnant and/or a subpopulation of male patients who are capable of impregnating female patients. Preferably, the counseling information discussed above relating to exposure of a fetus to a teratogenic drug may then be addressed primarily to this subpopulation of patients.

If the risk is considered to be acceptable, the patient may continue to receive the drug, using the methods described herein. If the risk is considered to be unacceptable, additional counseling may be provided to the patient or, if necessary, treatment of the patient with the involved drug may be terminated, with alternate treatment modalities being provided. In preferred embodiments, female patients will agree to complete a patient survey at least once every month, with male patients agreeing to complete a patient survey at least once every three to six months. The survey may be conducted by mail, facsimile transmission, on-line transmission or by telephone. Preferably, the survey is conducted by telephone through the use of an integrated voice response system (IVR).

After the patient has received counseling as described above, and has also filled out and signed an informed consent form, and it is determined that the drug which is to be prescribed is not contraindicated for the patient (such as, for example, a negative pregnancy test in the case of female

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patients for whom a prescription is desired for a teratogenic drug), the prescriber may prescribe the drug to the patient. In preferred embodiments of the present invention, the amount of the drug which is prescribed to the patient is for a limited amount, preferably no more than about 28 days. Refills for the drug will not be permitted without a renewal prescription from the prescriber, as discussed in detail below. In order to have the prescription filled, the patient preferably presents the prescription and the informed consent form to a pharmacy who has been registered, as discussed above. It is contemplated that the patient may bring the prescription to an unregistered pharmacy. If so, the pharmacy may take steps to become registered, for example, by immediately contacting the manufacturer of the drug. Once registration of the pharmacy is completed, the distribution procedure described herein may resume, per the discussion hereinafter. Of course, this may introduce a delay into the prescription process, and the patient may desire to take the prescription for the drug to an alternate, registered pharmacy. If the patient does not present a completed informed consent form to the pharmacy, or if verification of such informed consent has not previously been registered in the computer readable storage medium, the prescription may not be filled. In this case, pharmacy may contact the prescribing prescriber to have an informed consent form filled out for the patient.

The drug is preferably supplied to the pharmacy (as well as the patient) in packaging, such as individual blister packs, which includes warnings regarding the risks associated with the drug, as well as the importance of various aspects of the present methods such as, for example, pregnancy testing and the use of contraception (in the case of teratogenic drugs), and the dangers associated with sharing the drug with others, among other aspects.

As noted above, the drug is preferably prescribed and dispensed to the patient in a limited amount, with a prescription amount of no more than about 28 days being preferred, and preferably with no refills being permitted. Thus, for the patient to obtain an additional prescription, it is generally necessary for the patient to have a follow-up visit with the prescriber. Such a follow-up visit preferably takes place at least each time the patient requires a renewal of the prescription, and possibly more often if the patient requires, for example, additional counseling. At the follow-up visit, the patient will preferably receive additional counseling regarding the risks and benefits associated with taking the drug, as well as further counseling on birth control (if applicable). The patient will also preferably complete an additional patient survey to provide current information regarding their lifestyle, including their sexual behavior and, if female of child-bearing potential, be administered a new pregnancy test. After receiving the counseling and completing the patient survey, and if the pregnancy tests for female patients are negative, the prescriber may fill out a new prescription for the drug. As with the original prescription, the renewal prescription is preferably for a limited period of time, with no more than about 28 days being more preferred.

In certain embodiments, the prescriber may also receive reminders, for example, via mail, facsimile, or on-line transmission, from the manufacturer, distributor or other group or body providing oversight on drug distribution, that the prescriber has prescribed a hazardous drug to patients which may be contraindicated, and that the involved patients may require additional counseling and diagnostic testing. Such reminders may preferably be delivered to the prescriber, for example, from about 14 to about 21 days after the previous prescription was filled.

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As with the original prescription from the prescriber, the patient should present all renewal prescriptions to a registered pharmacy. Prior to filling out the prescription and dispensing the drug, the pharmacy preferably confirms, for example, via a standard on-line transmission or via telephone via IVR that the patient has been registered and is eligible to receive the drug. When patient eligibility has been confirmed, the pharmacy may dispense the drug to the patient. If the patient is ineligible, the pharmacy generally may not dispense the drug to the patient. The pharmacy may then contact, for example, the prescribing prescriber or the manufacturer of the drug to initiate patient registration. In preferred form, the pharmacy will be precluded from dispensing the drug if the patient has more than about 7 days of drug supply from the previous prescription, and/or if the new prescription was written more than about 14 days before the date the patient visits the pharmacy to have it filled.

The registration into one or more computer readable storage media of the prescriber, pharmacy and patient, according to the methods described herein, provide a means to monitor and authorize distribution of contraindicated drugs, including teratogenic drugs. Thus, the computer readable storage media may serve to deny access to, dispensing of, or prescriptions for contraindicated drugs, including teratogenic drugs, to patients, pharmacies or prescribers who fail to abide by the methods of the present invention. As noted above, prescribers who are not registered in a computer readable storage medium generally may not prescribe the drug, and pharmacies who are not registered generally may not dispense the drug. Similarly, the drugs generally may not be prescribed and/or dispensed to patients who are not registered in a computer readable storage medium. In addition, patients may be required to present an informed consent form to the pharmacy. Unless such a form is presented to the pharmacy, or verification of such informed consent has been provided by the prescriber and registered in the computer readable media, the patient generally may not receive the prescription for the drug. As noted above, only limited amounts of the drug may be prescribed to the patient, with no refill prescriptions being permitted.

In certain embodiments of the invention, the methods may require that the registered pharmacy consult the computer readable medium to retrieve a prescription approval code before dispensing the drug to the patient. This approval code is preferably not provided unless the prescriber, the pharmacy, the patient, the patient's risk group and the patient's informed consent have been properly registered in the storage medium. Additionally, depending upon the risk group assignment, generation of the prescription approval code may further require the registration in the storage medium of the additional set of information, including periodic surveys and the results of diagnostic tests, as have been defined as being relevant to the risk group assignment. Thus, to comply with the present methods and receive approval to dispense the drug as prescribed, the registered pharmacy need only retrieve the approval code. If the prescription approval code is not forthcoming, the patient may be directed to complete the necessary survey, for example, by telephone, or may be directed back to the prescriber for completion of necessary diagnostic tests. In this manner, the effort required by the pharmacy is minimized, and greater compliance with the present methods may efficiently and advantageously be achieved. Additionally, the embodiments described herein may provide greater assurance that all required further information, as is appropriate to the patient's risk group assignment, has been obtained before the drug is dispensed to the patient, and thereby minimize the risk that an adverse side effect will occur.

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While the delivery of teratogenic drugs is an aspect of the present invention which has clearly apparent benefit, other types of drugs may also beneficially be prescribed and delivered in accordance with one or more embodiments hereof and all are contemplated hereby. For example, the methods of the present invention may be used for delivery of a drug which is known or suspected of causing liver damage in many patients who take the drug. One such drug is isoniazid, a widely known treatment for tuberculosis (TB). In following a method of the present invention, a registered physician may wish to prescribe isoniazid to a patient who has tested positive for TB. The physician may register the patient in a computer readable storage medium, along with certain information regarding the patient's age, medical condition, and so on. If the patient is a young adult, for example, and presents with no other complicating risk factors, the patient may be assigned to a risk group that is designated to receive counseling regarding certain behavior, such as the concomitant use of alcohol, that is to be avoided. The patient may be fully informed of the risks of liver damage that may result from taking isoniazid, and is preferably counseled to avoid drinking any alcoholic beverages while undergoing treatment with the drug. Preferably, the patient signs an informed consent form, and the prescribing physician transmits verification of the informed consent, along with the patient's registration form and risk group assignment to the computer readable storage medium. The physician then provides the patient with a prescription for the isoniazid. Upon presentation of the prescription to a registered pharmacy, the computer readable storage medium is consulted to verify that the patient and prescriber are registered therein, and that the patient's risk group assignment and informed consent have been provided.

If the patient's risk group assignment so indicates, certain diagnostic tests may additionally be required, so that baseline data may be obtained, before the prescription will be approved for filling. The patient's risk group may indicate, for example, that serum liver enzymes should be evaluated on a monthly basis. Under these circumstances, the prescription will preferably be filled for no more than about 30 days.

The patient will also preferably be advised that completion of a monthly survey will be required. This survey may include a questionnaire which is probative of the patient's alcohol consumption over the past month. The survey may also include questions which are probative of certain symptoms which may be indicative of the early onset of liver damage or other side effects known or suspected of being caused by isoniazid. Additionally, questions regarding the patient's concomitant use of other drugs which are known to be hazardous when taken in combination with isoniazid, may be asked. Preferably, this survey is conducted telephonically, using an integrated voice response system, and the responses are entered in the storage medium. Based upon the patient's responses, the patient's risk group assignment is adjusted or left the same, as may be appropriate.

The patient is preferably further instructed that periodic diagnostic testing may also be necessary for continued approval of a prescription. Preferably, the diagnostic testing will include an assay of the patient's serum liver enzyme levels, to screen for early signs of liver damage. Additionally, the diagnostic testing may include screens for the presence of other drugs known to also cause liver damage, or to be hazardous if taken in combination with isoniazid. A prescription approval code generally will not be generated for subsequent prescriptions or refills until such periodic tests have been performed and satisfactory results entered into the computer readable storage medium. If a prescription approval code is

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not received by the pharmacy, the patient is directed to complete the requisite survey or tests, or to return to the doctor for further consultation.

If the test results or survey indicate that the risk of liver damage has increased, the patient's risk group assignment may be changed, or the patient will be directed to consult with the prescriber before any further isoniazid may be dispensed. In this way, the development of the adverse side effect of concern may be monitored. For example, if the tests indicate that some liver enzymes are marginally elevated, the patient's risk group status may be changed from a first risk group to a second risk group. As a member of this second risk group, the patient may be required to undergo additional diagnostic testing before approval will be given to receive the drug. Such testing may include, for example, liver function tests, to further diagnose the level of cellular damage potentially being caused by the isoniazid, or the combination of isoniazid and other drugs, such as alcohol. In more extreme cases, a diagnostic ultrasound of the liver, or even a liver biopsy may even be indicated. Ultimately, if the risk of continued administration becomes so great that it outweighs the possible benefits of continued treatment with isoniazid, the patient may be assigned to a risk group which indicates that the drug may no longer be dispensed to that patient.

The methods of the present invention may similarly be employed, for example, where the patient is undergoing treatment for infection with the Human Immunodeficiency Virus (HIV). Patients who test positive for HIV may be treated with one or more drugs to combat the onset of the Acquired Immune Deficiency Syndrome (AIDS). Frequently, HIV positive patients are administered an "AIDS cocktail" of several drugs including, for example, a combination of one or more inhibitors of viral protease and reverse transcriptase. By following the methods of the present invention, the patient may continue to receive the combination of drugs, while the risk of adverse side effects from administration of the drugs may be minimized. Additionally, the methods of the present invention may be desirably and advantageously used to educate and reinforce the actions and behaviors of patients who are taking a drug, as well as prescribers who prescribe the drug and pharmacies which dispense the drug.

As with methods of the invention previously described, when a patient has tested positive for HIV, a registered prescriber may obtain background information on the patient and see that a registration form is completed so that the patient may be registered in the computer readable storage medium. The prescriber may prescribe one or more drugs to the patient, including drugs which may be known or suspected of causing adverse side effects, either alone or in combination with each other or with other drugs. Depending upon the drugs prescribed, and also upon information which the prescriber will preferably obtain regarding the patient's medical history, physical condition and lifestyle, the patient will preferably be assigned to at least one risk group. Based upon this risk group assignment, the patient will preferably receive educational materials and counseling regarding the risks associated with the prescribed drugs, and be advised of the importance of the treatment regimen. The patient will also preferably receive counseling regarding the risk of spreading the disease to others, including a foetus which may be carried by the patient and any recipient of a bodily fluid of the patient. Thus, the patient may be counseled regarding the preferential use of one or more methods of birth control, and may also be provided with a contraceptive device by the prescriber. Additionally, the patient will preferably be counseled not to share any of the drugs with others, and to avoid taking any medications not prescribed. In this way, the patient will preferably be coun-

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seled both as to methods for minimizing the spread of the disease, as well as to methods for avoiding the occurrence of one or more side effects which may result from the taking of the medication. Preferably, upon full disclosure of all risks inherent in the treatment regimen, the prescriber will obtain and register in the computer readable storage medium the informed consent of the patient to receive the medication and to comply with the methods described herein for avoiding the occurrence of one or more side effects which may result from taking the drug or drugs prescribed.

To facilitate compliance with the methods of the present invention, and to minimize the likelihood of the occurrence of a known or suspected adverse side effect from treatment with the prescribed drug or drugs, it is preferable that when prescriptions for the drug are presented to a registered pharmacy, the computer readable storage medium is consulted to retrieve a prescription approval code before the drug is dispensed to the patient. In order for a prescription approval code to be generated, and based upon the patient's risk group assignment, the patient may be required to provide additional information, which may then be entered in the storage medium before approval of the prescription may be provided. For example, the patient may be required to undergo certain diagnostic tests. In a patient with HIV, for example, testing for viral load may be required, both initially and on a periodic basis, so that dosing of the medication may be adjusted, as necessary. The patient may also be required to complete a survey which asks questions probative of the likelihood that the patient is taking other medications, or beginning to exhibit symptoms which may be of importance to the selection and implementation of a therapeutic regimen. Such additional information may be required both before the initiation of treatment and on a periodic basis during treatment, as new prescriptions and prescription refills are generated. Based upon the information provided by the patient, and the results of any diagnostic tests which have been performed, the patient's risk group assignment may stay the same, or may be changed, as indicated. The patient's risk group assignment may also be changed based upon the length of time the patient has been receiving a given drug or medication.

A periodic patient survey may serve both to remind the patient of the requirements of the drug distribution program, and to obtain information which may be probative of the risk that an adverse side effect may occur. For example, the survey may include questions probative of the patient's behavior as it relates to the sharing of medication with other HIV positive individuals, and the patient's compliance with measures for avoiding the spread of the disease. Additionally, the survey may include questions regarding other drugs, medications or treatments which the patient might be availing themselves of, which would impact the risk of an adverse side effect occurring.

The survey may also contain questions which are probative of the onset of certain symptoms which may be indicative of the need for changes in the patient's treatment regimen. For example, some questions may be probative of the onset of depression in the patient, a common occurrence amongst AIDS sufferers. Answers to questions in the survey that are indicative of depression, for example, may cause the patient's risk group assignment to change such that the patient is directed to return to the prescriber for determination of whether treatment with an anti-depressant drug is indicated. Similarly, certain drugs, such as protease inhibitors, for example, may lead to abnormal redistribution of fat in certain patients. This symptom may be seen in conjunction with certain metabolic defects and may in turn be symptomatic of conditions such as high blood sugar and high cholesterol.

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Questions relating to this abnormality may be included on the survey, and answers which indicate that the patient has noticed such physical changes may lead to the assignment of the patient to a risk group in which diagnostic tests probative of the metabolic abnormalities are required before further access to the drug in question is permitted.

As with the survey, the diagnostic testing which the patient may be required to undergo may vary with, and preferably is appropriate to, the patient's risk group assignment. In addition to testing for the patient's viral load, periodic diagnostic testing may be appropriate, for example, to evaluate the level of one or more medications in the patient. Dosage of reverse transcriptase inhibitors, for example, may be critical to the risk of occurrence of an adverse side effect. At the same time, various drugs which are often used in combination may share similar metabolic pathways, so that the addition of a second drug to the treatment regimen may greatly affect the pharmacokinetics of the first drug, thereby necessitating an adjustment in the dose of the first drug. In the case of treatment with an "AIDS cocktail" containing, for example, the use of ritonavir, a well-known protease inhibitor, may greatly impact the bioavailability of other protease inhibitors, requiring that the dose of the other protease inhibitors be reduced. Accordingly, the inclusion of ritonavir in the patient's treatment regimen may initiate a change in risk-group assignment, which in turn requires that diagnostic testing to evaluate the blood levels of other concomitantly administered protease inhibitors be done on a periodic basis.

Similarly, the addition of other drugs to the treatment regimen, either by the prescribing physician, or by another physician whom the patient might visit, may interfere with the initial treatment regimen prescribed by the registered prescriber. For example, AIDS patients often develop mycobacterial infections such as tuberculosis. An infectious disease specialist may prescribe one of a class of drugs known as rifamycins, such as rifampin or rifabutin, to treat such infections. Rifamycins are known to accelerate the metabolism of many protease inhibitors, however, so that upon initiation of treatment with a rifamycin, the effectiveness of the protease inhibitors may be greatly reduced, unless the dosage of those drugs is adjusted appropriately. Thus, when the patient is being treated with a protease inhibitor, the survey may include, for example, questions regarding the possible concurrent use of a rifamycin. If the survey results indicate that the two types of drugs are being used concurrently, the patient's risk group assignment is changed, such that the patient may be referred back to the prescriber for an adjustment in dosage, or the patient may be directed to undergo diagnostic testing to assure that a sufficient level of the protease inhibitor is still being maintained. Similarly, where the registered prescriber adds a prescription for a rifamycin to the treatment regimen of a registered patient who is also receiving a protease inhibitor, entry of the prescription into the computer readable storage medium may trigger an automatic change in risk group assignment, such that approval of the prescription will not be generated without further modification of the dosage of the protease inhibitor. In this way, the methods of the present invention may be advantageously utilized to maintain the proper dosing of one or more drugs, to minimize the likelihood of the occurrence of an adverse side effect from the concomitant use of such drugs, or the addition of other drugs to a treatment regimen, to encourage proper disclosure of the risks associated with the taking of one or more drugs, to minimize the risk that a contraindicated individual will be exposed to the potentially hazardous drugs, and to assist in generating patient compliance with treatment pro-

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ocols and avoidance of behavior known to increase the risk that the disease will be spread to others.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

What is claimed:

1. A system for communicating over a network with a pharmacist for authorizing delivery of a contraindicated drug to a patient, the patient pre-assigned to at least one risk group of a plurality of risk groups, the plurality of risk groups defined based on factors which indicate one or more risks of one or more adverse side effects if the patient receives the drug, the system comprising:

a computer device including:

a computer readable medium having stored therein the plurality of risk groups, the at least one risk group assignment, and registration information of the patient;

the computer device configured to provide:

an interface configured to receive an on-line transmission of a pharmacist prescription for the patient in order to dispense the contraindicated drug to the patient;

a generator configured to generate a prescription approval code based on comparison of the on-line transmission of the pharmacist prescription for the patient with the registration information of the patient stored in the computer readable medium to confirm if the patient is registered, and based on comparison of the on-line transmission of the pharmacist prescription for the patient with the risk group assignment stored in the computer readable medium to determine if the patient is eligible to receive the contraindicated drug, such that the risk group assignment is based on a predefined set of risk parameters for the contraindicated drug; and

an interface configured to send an on-line transmission to the pharmacist including the generated prescription approval code when the registered patient is eligible to receive the drug;

wherein the pharmacist can proceed with dispensation of the drug to the patient on the basis of the generated prescription approval code once received.

2. The system of claim 1 further comprising the computer readable medium having stored thereon further information selected from the group comprising: registration of the pharmacist as qualified to fill a prescription for the drug and registration of a prescriber as qualified to prescribe the drug.

3. The system of claim 2, wherein the further information includes an informed consent of the patient for receiving the drug.

4. The system of claim 3, wherein the further information is compared with the drug request before generation of the prescription approval code.

5. The system of claim 4, wherein the patient registration information includes information selected from the group comprising: name; age; sex; mailing address; date of birth; specified prescriber for the drug; history of drug prescription; medical condition; medical patient history; and lifestyle.

6. The system of claim 4, wherein the drug is a teratogen intended for prescription for activity selected from the group comprising: disease diagnosis; disease cure; disease mitigation; disease treatment or prevention; and to affect the structure or function of the body of the patient.

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7. The system of claim 4, wherein the one or more adverse side effects of the drug is selected from the group comprising: abnormality; defect; mutation; lesion; degeneration; and injury.

8. The system of claim 7, wherein an individual having the one or more risks of the one or more adverse side effects is selected from the group comprising: the patient, a foetus of the patient, and a foetus carried by a recipient of bodily fluid of the patient.

9. The system of claim 8, wherein the drug is one of a plurality of drugs available to the patient and the one or more risks of the one or more adverse side effects is defined in the risk group assignment as from a combination of the plurality of drugs.

10. The system of claim 1 further comprising additional communication over the network via on-line communication.

11. The system of claim 10 further comprising the interface including an integrated voice response system such that the network is a telecommunications network.

12. The system of claim 1 computer readable medium having stored thereon risk parameters assigned to the plurality of risk groups, such that the at least one risk group includes a risk parameter selected from the group comprising: female patients of child bearing potential; female patients of non-child bearing potential; sexually active male patients; sexually inactive male patients; patients to whom administration of the drug may be strictly contraindicated; factors influencing a likelihood that certain pre-existing conditions may exist; and factors indicating a likelihood of certain other drugs being used concomitantly with the drug.

13. The system of claim 12 further comprising the on-line transmission to the pharmacist such that the generated prescription approval code is omitted from the on-line transmission to the pharmacist and a request for additional information is included in the on-line transmission to the pharmacist, the additional information selected from the group comprising: a survey for a set of information to be collected from the patient that is probative of the one or more risks of the one or more adverse side effects to occur if the drug is provided to the patient; and a diagnostic test result associated with the patient.

14. The system of claim 13, wherein the diagnostic test result is selected from the group comprising: genetic test results; pregnancy test results; and evidence of use of another drug different from the drug of the on-line transmission of the pharmacist prescription.

15. The system of claim 13 further configured such that the least one risk group assigned to the patient defines the additional information for the request for additional information included in the on-line transmission to the pharmacist.

16. The system of claim 15, wherein the additional information is defined for updating parameters of the patient risk group assignment on a periodic basis.

17. The system of claim 16, wherein the providing of the additional information to the computer readable medium results in an update of the patient risk group assignment.

18. The system of claim 15 further comprising the interface configured for providing the generated approval code once the registered patient is deemed eligible to receive the drug in view of the update to the patient risk group assignment.

19. The system of claim 12, wherein the on-line transmission of the pharmacist prescription is selected from the group comprising: an initial prescription for the drug and a prescription refill for the drug.

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20. The system of claim 19, wherein additional information when received by the interface in reply to the request for additional information is stored in the computer readable medium.

21. A method for communicating over a network with a pharmacist for authorizing delivery of a contraindicated drug to a patient, the patient pre-assigned to at least one risk group of a plurality of risk groups, the plurality of risk groups defined based on factors which indicate one or more risks of one or more adverse side effects if the patient receives the drug, the method comprising the steps of:

accessing, using a computer device, a computer readable medium having stored thereon the plurality of risk groups, the at least one risk group assignment, and registration information for the patient in computer readable medium;

receiving, using the computer device, an on-line transmission of a pharmacist prescription for the patient in order to dispense the contraindicated drug to the patient;

comparing, using the computer device, the on-line transmission of the pharmacist prescription for the patient with the registration information of the patient stored in the computer readable medium to confirm if the patient is registered, and comparing of the on-line transmission of the pharmacist prescription for the patient with the risk group assignment stored in the computer readable medium to determine if the patient is eligible to receive the contraindicated drug,

generating, using the computer device, a prescription approval code based on comparison of the on-line transmission of the pharmacist prescription for the patient if confirmed the registered patient is eligible to receive the drug; and

sending, using the computer device, an on-line transmission to the pharmacist including the generated prescription approval code when the registered patient is eligible to receive the drug;

wherein the pharmacist can proceed with dispensation of the drug to the patient on the basis of the generated prescription approval code once received.

22. The method of claim 21 further comprising the step of storing further information selected from the group comprising: registration of the pharmacist as qualified to fill a prescription for the drug and registration of a prescriber as qualified to prescribe the drug.

23. The method of claim 22, wherein the further information includes an informed consent of the patient for receiving the drug.

24. The method of claim 23, wherein the further information is compared with the drug request before generation of the prescription approval code.

25. The method of claim 24, wherein the patient registration information includes information selected from the group comprising: name; age; sex; mailing address; date of birth; specified prescriber for the drug; history of drug prescription; medical condition; medical patient history; and lifestyle.

26. The method of claim 24, wherein the drug is a teratogen intended for prescription for activity selected from the group comprising: disease diagnosis; disease cure; disease mitigation; disease treatment or prevention; and to affect the structure or function of the body of the patient.

27. The method of claim 24, wherein the one or more adverse side effects of the drug is selected from the group comprising: abnormality; defect; mutation; lesion; degeneration; and injury.

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28. The method of claim 27, wherein an individual having the one or more risks of the one or more adverse side effects is selected from the group comprising: the patient, a foetus of the patient, and a foetus carried by a recipient of bodily fluid of the patient.

29. The method of claim 28, wherein the drug is one of a plurality of drugs available to the patient and the one or more risks of the one or more adverse side effects is defined in the risk group assignment as from a combination of the plurality of drugs.

30. The method of claim 21 further comprising additional communication over the network via on-line communication.

31. The method of claim 30, wherein the receiving of the on-line transmission of the pharmacist prescription is via an integrated voice response system such that the network is a telecommunications network.

32. The method of claim 21 further comprising the step of storing risk parameters assigned to the plurality of risk groups, such that the at least one risk group includes a risk parameter selected from the group comprising: female patients of child bearing potential; female patients of non-child bearing potential; sexually active male patients; sexually inactive male patients; patients to whom administration of the drug may be strictly contraindicated; factors influencing a likelihood that certain pre-existing conditions may exist; and factors indicating a likelihood of certain other drugs being used concomitantly with the drug.

33. The method of claim 32 further comprising the step of omitting the generated prescription approval code from the on-line transmission to the pharmacist and including a request for additional information in the on-line transmission to the pharmacist, the additional information selected from the group comprising: a survey for a set of information to be

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collected from the patient that is probative of the one or more risks of the one or more adverse side effects to occur if the drug is provided to the patient; and a diagnostic test result associated with the patient.

34. The method of claim 33, wherein the diagnostic test result is selected from the group comprising: genetic test results; pregnancy test results; and evidence of use of another drug different from the drug of the on-line transmission of the pharmacist prescription.

35. The method of claim 33, wherein the least one risk group assigned to the patient defines the additional information for the request for additional information included in the on-line transmission to the pharmacist.

36. The method of claim 35 further comprising the step of using the additional information obtained from the patient for updating parameters of the patient risk group assignment on a periodic basis.

37. The method of claim 36 further comprising the step of using the additional information to update the patient risk group assignment.

38. The method of claim 35 further comprising the step of providing the generated prescription approval code once the registered patient is deemed eligible to receive the drug in view of the update to the patient risk group assignment.

39. The method of claim 32, wherein the on-line transmission of the pharmacist prescription is selected from the group comprising: an initial prescription for the drug and a prescription refill for the drug.

40. The method of claim 39 further comprising the step of storing the additional information in the computer readable medium when received in reply to the request for additional information.

* * * * *

EXHIBIT F

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(12) **United States Patent**
Jaworsky et al.

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(45) **Date of Patent:** **Dec. 16, 2008**

(54) **POLYMORPHIC FORMS OF
3-(4-AMINO-1-OXO-1,3
DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-
2,6-DIONE**

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5,059,595 A	10/1991	Le Grazie
5,073,543 A	12/1991	Marshall et al.
5,120,548 A	6/1992	McClelland et al.
5,229,496 A	7/1993	Deeley et al.
5,354,556 A	10/1994	Sparks et al.
5,385,901 A	1/1995	Kaplan et al.
5,391,485 A	2/1995	Deeley et al.
5,393,870 A	2/1995	Deeley et al.
5,528,823 A	6/1996	Rudy, Jr. et al.
5,580,755 A	12/1996	Souza
5,591,767 A	1/1997	Mohr et al.
5,593,990 A	1/1997	D'Amato
5,629,327 A	5/1997	D'Amato
5,635,517 A	6/1997	Muller et al.

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(Continued)

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FOREIGN PATENT DOCUMENTS

WO WO 98/03502 1/1998

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4, 2003.

(Continued)

OTHER PUBLICATIONS

(51) **Int. Cl.**
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Seddon "Pseudopolymorph: a polemic" Crystal Growth & design
v.4(6) 1087, Web release Oct. 19, 2004.*

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(58) **Field of Classification Search** **546/200;**
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(56) **References Cited**

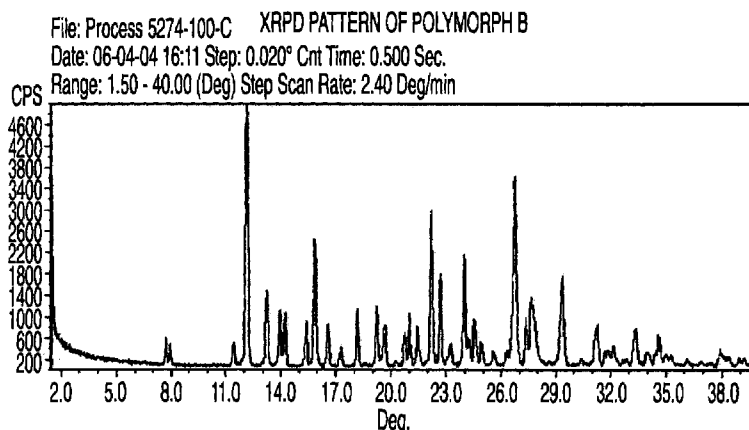
(57) **ABSTRACT**

U.S. PATENT DOCUMENTS

3,536,809 A	10/1970	Applezweig
3,598,123 A	8/1971	Zaffaroni et al.
3,845,770 A	11/1974	Theeuwes et al.
3,916,899 A	11/1975	Theeuwes et al.
4,008,719 A	2/1977	Theeuwes et al.
4,810,643 A	3/1989	Souza
4,999,291 A	3/1991	Souza

Polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoin-
dol-2-yl)-piperidine-2,6-dione are disclosed. Compositions
comprising the polymorphic forms, methods of making the
polymorphic forms and methods of their use are also dis-
closed.

14 Claims, 48 Drawing Sheets



US 7,465,800 B2

Page 2

U.S. PATENT DOCUMENTS

5,639,476	A	6/1997	Oshlack et al.
5,674,533	A	10/1997	Santus et al.
5,698,579	A	12/1997	Muller
5,712,291	A	1/1998	D'Amato
5,731,325	A	3/1998	Andrulis, Jr. et al.
5,733,566	A	3/1998	Lewis
5,798,368	A	8/1998	Muller et al.
5,874,448	A	2/1999	Muller et al.
5,877,200	A	3/1999	Muller
5,929,117	A	7/1999	Muller et al.
5,955,476	A	9/1999	Muller et al.
6,020,358	A	2/2000	Muller et al.
6,071,948	A	6/2000	D'Amato
6,114,355	A	9/2000	D'Amato
6,140,346	A	10/2000	Andrulis, Jr. et al.
6,235,756	B1	5/2001	D'Amato
6,281,230	B1	8/2001	Muller et al.
6,316,471	B1	11/2001	Muller et al.
6,326,388	B1	12/2001	Man et al.
6,335,349	B1	1/2002	Muller et al.
6,380,239	B1	4/2002	Muller et al.
6,395,754	B1	5/2002	Muller et al.
6,403,613	B1	6/2002	Man et al.
6,420,414	B1	7/2002	D'Amato
6,458,810	B1	10/2002	Muller et al.
6,469,045	B1	10/2002	D'Amato
6,476,052	B1	11/2002	Muller et al.
6,518,298	B2	2/2003	Green et al.
6,555,554	B2	4/2003	Muller et al.
2001/0018445	A1	8/2001	Huang et al.
2001/0056114	A1	12/2001	D'Amato
2002/0035090	A1	3/2002	Zeldis et al.
2002/0045643	A1	4/2002	Muller et al.
2002/0052398	A1	5/2002	D'Amato
2002/0054899	A1	5/2002	Zeldis
2002/0061923	A1	5/2002	D'Amato
2002/0128228	A1	9/2002	Hwu
2002/0161023	A1	10/2002	D'Amato
2002/0173658	A1	11/2002	Muller et al.
2002/0183360	A1	12/2002	Muller et al.
2003/0013739	A1	1/2003	Masferrer et al.
2003/0028028	A1	2/2003	Man et al.
2003/0045552	A1	3/2003	Robarge et al.
2003/0069428	A1	4/2003	Muller et al.
2003/0096841	A1	5/2003	Robarge et al.
2003/0139451	A1	7/2003	Shah et al.
2003/0144325	A1	7/2003	Muller et al.
2003/0181428	A1	9/2003	Green et al.
2003/0187024	A1	10/2003	D'Amato
2003/0191098	A1	10/2003	D'Amato
2003/0235909	A1	12/2003	Hariri et al.
2004/0029832	A1	2/2004	Zeldis
2004/0077685	A1	4/2004	Figg et al.
2004/0077686	A1	4/2004	Dannenberg et al.
2004/0087546	A1	5/2004	Zeldis
2004/0091455	A1	5/2004	Zeldis
2004/0122052	A1	6/2004	Muller et al.
2004/0220144	A1	11/2004	Zeldis
2004/0266809	A1	12/2004	Emanuel et al.

FOREIGN PATENT DOCUMENTS

WO	WO 98/54170	12/1998
WO	WO 01/70275	9/2001
WO	WO 01/87307	11/2001
WO	WO 02/059106	8/2002
WO	WO 02/064083	8/2002
WO	PCT/US03/11578	1/2003

OTHER PUBLICATIONS

Chen et al. "Polymorphic forms of . . ." CA 142:303619 (2005).*

Haleblian, J.; McCrone, W.; *Pharmaceutical Applications of Polymorphism*, Journal of Pharmaceutical Sciences, vol. 58., No. 8, Aug. 1969.

U.S. Appl. No. 60/372,348, Hariri et al.

U.S. Appl. No. 10/732,867, D'Amato et al.

U.S. Appl. No. 09/545,654, D'Amato.

U.S. Appl. No. 09/287,377, D'Amato.

Anderson, "Moving disease biology from the laboratory to the clinic," *Seminars in Oncology*, 2002 29:17-20.

Barlogie et al., "High-dose therapy immunomodulatory drugs in multiple myeloma," *Seminars in Oncology*, 2002, 29 (6):26-33.

Barlogie et al., "Introduction: Thalidomide and the IMiDs in multiple myeloma," *Seminars in Hematology*, 2003, 40 (4):1-2.

Barlogie et al., "Total Therapy II (TII) for newly diagnosed multiple myeloma (MM): preliminary data on feasibility and efficacy in the first 231 enrolled patients; comparison with predecessor trial total therapy I (TTI) (N=231)," *Blood*, Abstract # 2857, Dec. 7-11, 2001, *American Society of Hematology*.

Barlogie, "Thalidomide and CC-5013 in Multiple Myeloma: The University of Arkansas experience," *Seminars in Hematology*, 2003, 40 (4):33-38.

Bartlett et al., "Phase I study to determine the safety, tolerability and immunostimulatory activity of thalidomide analogue CC-5013 in patients with metastatic malignant melanoma and other advanced cancers," *British Journal of Cancer*, 2004, 90:955-961.

Bartlett et al., "The evolution of thalidomide and its IMiD derivatives as anticancer agents," *Nature Reviews Cancer*, 2004, 4 (4):1-9.

Battegay, "Angiogenesis: mechanistic insights, neovascular diseases, and therapeutic prospects," *J. Mol. Med.*, 1995, 73:333-346.

Baz et al., "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and revlimid (R) (DvD-R) results in a high response rate in patients with refractory multiple myeloma (RMM)," *Blood*, Abstract # 2559, *American Society of Hematology*, Dec. 10-13, 2005.

Brennen et al., "Thalidomide and analogues: current proposed mechanisms and therapeutic usage," *Clinical Prostate Cancer*, 2004, 3 (1):54-61.

Celgene Corporation, "Additional clinical data presented on Revimid™ in myelodysplastic syndromes at the American Society of Hematology 45th annual meeting," Press Release, Dec. 2003.

Celgene Corporation, "Blood reports Revimid™ has anti-tumor activity in patients with relapsed and refractory multiple myeloma," Press Release, Nov. 1, 2002.

Celgene Corporation, "Celgene advances immunomodulatory drug (IMiD™) clinical program," Press Release, Feb. 2000.

Celgene Corporation, "Celgene announces plans to stop phase III trials in melanoma due to lack of efficacy," Press Release, Apr. 2004.

Celgene Corporation, "Celgene corporation advances ACTIMID™ (CC-4047) into phase II trial for prostate cancer," Press Release, Oct. 2003.

Celgene Corporation, "Celgene Corporation announces fourth quarter and full year results for 2002," Press Release, Jan. 2003.

Celgene Corporation, "Celgene Corporation announces third quarter results. THALOMID® (thalidomide) revenue increases 41% to \$30.5 million. Pivotal programs for THALOMID and REVIMID™ finalized. Peer-reviewed publications of THALOMID and REVIMID data. First JNK inhibitor advanced to Phase I clinical trial," Press Release, Oct. 2002.

Celgene Corporation, "Celgene Corporation announces third quarter results. Thalomid® (thalidomide) sales increase 24%. Prescriptions up 50%. Enhanced S.T.E.P.S.® launched. Pilot d-MPH data presented," Press Release, Oct. 2001.

Celgene Corporation, "Celgene Corporation receives orphan drug designation for Revimid™ for multiple myeloma," Press Release, Oct. 2001.

Celgene Corporation, "Celgene corporation reports record operating performance in first quarter with strong revenue growth and profits," Press Release, Apr. 2004.

Celgene Corporation, "Celgene corporation reports record operating performance in third quarter as total revenue increases 117% and profits rise," Press Release, Oct. 2003.

US 7,465,800 B2

Page 3

- Celgene Corporation, "Celgene corporation reports strong operating performance in second quarter as total sales increase 100 percent and profits rise," Press Release, Jul. 2003.
- Celgene Corporation, "Celgene corporation reviews 2003 achievements and announces 2004 financial outlook," Press Release, Jan. 2004.
- Celgene Corporation, "Celgene expands clinical development program for Revimid™. Five additional trials of Revimid initiated in hematological and solid tumors cancers," Press Release, Jun. 2002.
- Celgene Corporation, "Celgene provides update on clinical pipeline. Celgene Announces first target indication for ACTIMID™, CC-8490. SelCID™ program to advance based on results from Phase I/II trial of CC-1088. First JNK inhibitor successfully completes phase I trial," Press Release, Jan. 2003.
- Celgene Corporation, "Celgene receives fast track status from FDA for Revimid™ in multiple myeloma," Press Release, Feb. 2003.
- Celgene Corporation, "Celgene receives fast track status from FDA for Revimid™ in myelodysplastic syndromes," Press Release, Apr. 2003.
- Celgene Corporation, "Initial Phase I solid tumor data on Celgene's lead IMiD™, Revimid™," Press Release, Jun. 2001.
- Celgene Corporation, "New Revimid™ clinical data shows potential as novel approach to treating myelodysplastic syndromes (MDS)," Press Release, May 2003.
- Celgene Corporation, "Revlimid™ receives orphan drug designation from the European commission for multiple myeloma," Press Release, Feb. 2004.
- Celgene Corporation, "Revlimid™ receives orphan drug designation from the European commission for myelodysplastic syndromes," Press Release, Mar. 2004.
- Chaundhry, 1966, *Cancer Research*, "Effect of Prednisolone and Thalidomide on Induced Submandibular Gland Tumors in Hamster," 26(part 1):1884-86.
- Corral et al., 1999, "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha," *J. Immunol.* 163(1):380-386.
- Craig et al., 1967, "Potential anticancer agents. III. 2-phthalimidoaldehydes and derivatives," *Potential Anticancer Agents* III 10:1071-1073.
- D'Amato et al., 2001, "Mechanism of action of thalidomide and 3-aminothalidomide in multiple myeloma," *Semin. Oncol.* 28:597-601.
- Dalgleish et al., "Thalidomide analogues CC-5013 and CC-4047 induce T cell activation and IL-12 production in patients with both solid tumours and relapsed and refractory multiple myeloma," *British Journal of Cancer*, 2003, 88(Suppl 1), S25-S54.
- Dalgleish, et al., "New thalidomide analogues; anti-cancer, anti-angiogenic and immunostimulatory," *British Journal of Cancer*, 2001, 85 (1):25.
- Davies et al., "Thalidomide (Thal) and immunomodulatory derivatives (IMiDs) augment natural killer (NK) cell cytotoxicity in multiple myeloma-MM," Abstract # P222, *VIIIth International Myeloma Workshop*, May 4-8, 2001.
- Davies et al., "Thalidomide (Thal) and immunomodulatory derivatives (IMiDs) augment natural killer (NK) cell cytotoxicity in multiple myeloma-MM," Abstract # 3617, *American Society of Hematology*, Dec. 1-5, 2000.
- Davies et al., 2001, "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma," *Blood* 98(1):210-216.
- Dibbs et al., "Thalidomide and thalidomide analogs suppress TNF α secretion by myocytes," Abstract # 1284, *Circulation*, 1998.
- Dimopoulos et al., "Results of thalidomide and IMiDs in multiple myeloma," Abstract # P12.1.4, *International Multiple Myeloma Workshop*, May 23-27, 2003.
- Dimopoulos et al., "Study of lenalidomide plus dexamethasone versus dexamethasone alone in relapsed or refractory multiple myeloma (MM): Results of a phase 3 Study (MM-010)," Abstract # 6, *American Society of Hematology*, Dec. 10-13, 2005.
- Dimopoulos et al., "Treatment of plasma cell dyscrasias with thalidomide and its derivatives," *Journal of Clinical Oncology*, Dec. 1, 2003, 21 (23):4444-4454.
- Dimopoulos et al., 2004, "Primary treatment with pulsed melphalan, dexamethasone, thalidomide (MDT) for symptomatic patients with multiple myeloma ≥ 75 years of age," *Am. Soc. Hematol.* 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract #1482.
- Dredge et al., "A costimulatory thalidomide analog enhances the partial anti-tumor immunity of an autologous vaccination in a model of colorectal cancer, Abstract # 491, *American Association for Cancer Research*, Apr. 6-10, 2002.
- Dredge et al., "Adjuvants and the promotion of Th1-type cytokines in tumour immunotherapy," *Cancer Immunol. Immunother.*, 2002, 51:521-531.
- Dredge et al., "Angiogenesis inhibitors in cancer therapy," *Current Opinion in Investigational Drugs*, 2003, 4 (6):667-674.
- Dredge et al., "Immunological effects of thalidomide and its chemical and functional analogs," *Critical Reviews in Immunology*, 2002, 22 (5&6):425-437.
- Dredge et al., "Protective antitumor immunity induced by a costimulatory thalidomide analog in conjunction with whole tumor cell vaccination is mediated by increased Th1-type immunity¹," *The Journal of Immunology*, 2002, 168:4914-4919.
- Dredge et al., "Recent developments in antiangiogenic therapy," *Expert Opin. Biol. Ther.*, 2002, 2 (8):953-966.
- Dredge et al., "Thalidomide analogs as emerging anti-cancer drugs," *Anti-Cancer Drugs*, 2003, 14:331-335.
- Dredge et al., 2002, "Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects," *Br. J. Cancer* 87(10):1166-1172.
- Fickentscher et al., "Stereochemical properties and teratogenic activity of some tetrahydrophthalimides," *Molecular Pharmacology*, 1976, 13:133-141.
- Galustian et al., "Thalidomide-derived immunomodulatory drugs as therapeutic agents," *Expert Opin. Biol. Ther.*, 2004, 4 (12):1-8.
- Glaspy et al., "The potential role of thalidomide and thalidomide analogs in melanoma," *Clinical Advances in Hematology & Oncology*, 2004, 1-7.
- Gupta et al., "Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications," *Leukemia*, 2001, 15:1950-1961.
- Haslett et al., 2003, "Thalidomide and a thalidomide analogue drug costimulate virus-specific CD8⁺ T cells in vitro," *J. Infect. Dis.* 187(6):946-955.
- Hayashi et al., "Mechanisms whereby immunomodulatory analogs of thalidomide augment autologous NK cell anti-myeloma immunity," *Blood*, Abstract #3219, Dec. 6-10, 2002, *American Society of Hematology*.
- He, W., et al., 1993, Abstract of papers, 206th American Chemical Society, Chicago, IL: Med. Chem., paper 216.
- Helm et al., "Comparative teratological investigation of compounds of structurally and pharmacologically related to thalidomide," *Arzneimittel Forschung/Drug Research*, 1981, 31 (I):941-949.
- Hernandez-Illizaliturri et al., "Addition of immunomodulatory drugs CC5013 or CC4047 to rituximab enhances anti-tumor activity in a severe combined immunodeficiency (SCID) mouse lymphoma model," Abstract # 235, *American Society of Hematology*, Dec. 6-9, 2003.
- Hideshima et al., "Thalidomide (Thal) and its analogs overcome drug resistance of human multiple myeloma (MM) cells to conventional therapy," Abstract 1313, *American Society of Hematology*, Dec. 1-5, 2000.
- Hideshima et al., "Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy," *Blood*, 2000, 96:2943-2950, *American Society of Hematology*.
- Hunt et al., "Markers of endothelial and haemostatic activation in the use of CC-4047, a structural analogue of thalidomide, in relapsed myeloma," *Blood*, Abstract # 3216, Dec. 6-10, 2002, *American Society of Hematology*.
- Hussein et al., "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and Revlimid (DVd-R) a phase I/II trial in advanced relapsed/refractory multiple myeloma (Rmm) patients," *Blood*, Abstract #208, *American Society of Hematology*, Dec. 4-7, 2004.
- Kyle et al., "Multiple myeloma," *New England Journal of Medicine*, 2004, 351:1860-1873.

US 7,465,800 B2

Page 4

- Kyle, "Current therapy of multiple myeloma," *Internal Medicine*, 2002, 41 (3):175-180.
- Leblanc et al., "Immunomodulatory drug costimulates T cells via the B7-CD28 pathway," *Blood*, 2004, 103:1787-1790, *American Society of Hematology*.
- Lentzsch et al., "Immunomodulatory derivative of thalidomide (IMiD CC-4047) determine the lineage commitment of hematopoietic progenitors by down regulation of GATA-1 and modulation of cytokine secretion," Abstract # 3073, *American Society of Hematology*, Dec. 6-9, 2003.
- Lentzsch et al., "Immunomodulatory derivative of thalidomide (IMiD CC-4047) down regulates CAAT/enhancer-binding protein β (C/EBP β) in multiple myeloma (MM)," Abstract # 3456, *American Society of Hematology*, Dec. 6-9, 2003.
- Lentzsch et al., "In vivo activity of thalidomide and immunomodulatory drugs against multiple myeloma," *VIIIth International Myeloma Workshop*, Abstract #P225, May 4-8, 2001.
- Lentzsch et al., 2003, "Immunomodulatory analogs of thalidomide inhibit growth of Hs Sultan cells and angiogenesis in vivo," *Leukemia* 17(1):41-44.
- Liu et al., "Phase I study of CC-5013 (Revimid), a thalidomide derivative, in patients with refractory metastatic cancer," *American Society of Clinical Oncology*, Abstract #927, 2003.
- Luzzio et al., "Thalidomide analogues: derivatives of an orphan drug with diverse biological activity," *Expert Opin. Ther. Patents*, 2004, 14 (2):215-229.
- Man et al., " α -Fluoro-substituted thalidomide analogues," *Bioorganic & Medicinal Chemistry Letters* 13, 2003, 3415-3417.
- Marriott et al., "A novel subclass of thalidomide analogue with anti-solid tumor activity in which caspase-dependent apoptosis is associated with altered expression of bcl-2 family proteins," *Cancer Research*, 2003, 63:593-599.
- Marriott et al., "Immunotherapeutic and antitumour potential of thalidomide analogues," *Expert Opin. Biol. Ther.*, 2001, 1 (4):1-8.
- Marriott et al., "New thalidomide analogues; anti-cancer, anti-angiogenic and immunostimulatory," *British Journal of Cancer*, 85:25, Jul. 6, 2001.
- Marriott et al., "Thalidomide and its analogues have distinct and opposing effects on TNF- α and TNFR2 during co-stimulation of both CD4⁺ and CD8⁺ T cells," *Clin. Exp. Immunol.*, 2002, 130:75-84.
- Marriott et al., "Thalidomide derived immunomodulatory drugs (IMiDs) as potential therapeutic agents," *Current Drug Targets—Immune, Endocrine & Metabolic Disorders*, 2003, 3:181-186.
- Masellis et al., "Changes in gene expression in bone marrow mesenchymal progenitor cells as a consequence of IMiD therapy in multiple myeloma patients," *Blood*, Abstract # 1548, Dec. 7-11, 2001, *American Society of Hematology*.
- McCarty, "Thalidomide may impede cell migration in primates by down-regulating integrin β -chains: potential therapeutic utility in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis," *Medical Hypotheses*, 1997, 49:123-131.
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs (ImiDs) in human multiple myeloma cells: therapeutic implications," Abstract # 3224, Dec. 7-11, 2001, *American Society of Hematology*.
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications," *Blood*, 2002, 99:4525-4530, *American Society of Hematology*.
- Mitsiades et al., "CC-5013 Celgene," *Current Opinion in Investigational Drugs*, 2004, 5 (6):635-647.
- Miyachi et al., 1997, "Novel biological response modifiers: phthalimides with tumor necrosis factor- α production-regulating activity," *J. Med. Chem.* 40:2858-2865.
- Moutouh et al., "Novel immunomodulatory drugs (IMiDs®): A potential, new therapy for β -hemoglobinopathies," Abstract # 3740, *American Society of Hematology*, Dec. 4-7, 2004.
- Patten et al., "The early use of the serum free light chain assay in patients with relapsed refractory myeloma receiving treatment with a thalidomide analogue (CC-4047)," Abstract # 1640, *American Society of Hematology*, Dec. 6-9, 2003.
- Payvandi et al., "CC-5013 inhibits the expression of adhesion molecules ICAM-1 and CD44 and prevents metastasis of B16 F10 mouse melanoma cells in an animal model," *American Society of Clinical Oncology*, Abstract # 992, 2003.
- Payvandi et al., "Effects of a thalidomide analog on binding activity of transcription factors and cell cycle progression of multiple myeloma cell lines," *Blood*, Abstract #2487, Dec. 1-5, 2000, *American Society of Hematology*.
- Payvandi et al., "Immunomodulatory drugs inhibit expression of cyclooxygenase-2 from TNF- α , IL-1 β , and LPS-stimulated human PBMC in a partially IL-10-dependent manner," *Cellular Immunology*, 2004, 81-88.
- Payvandi et al., "Thalidomide and IMiDs inhibit microvessel formation from human arterial rings in the absence of human liver microsomes," *Blood*, Abstract # 5046, Dec. 6-10, 2002, *American Society of Hematology*.
- Payvandi et al., "Thalidomide analogs IMiDs inhibit expression of cyclooxygenase-2 in multiple myeloma cell line and LPS stimulated PBMCs," *Blood*, Abstract # 2689, Dec. 7-11, 2001, *American Society of Hematology*.
- Payvandi et al., "The thalidomide analogs IMiDs enhance expression of CD69 stimulatory receptor on natural killer cells," Abstract # 1793, *American Association for Cancer Research*, Mar. 24-28, 2001.
- Raje et al., "Combination of the mTOR inhibitor rapamycin and CC-5013 has synergistic activity in multiple myeloma," *Blood*, Dec. 15, 2005, 104 (13):4188-4193.
- Rajkumar et al., "Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma," *Blood*, Dec. 15, 2005, 106 (13):4050-4053.
- Richardson et al., "A multi-center, randomized, phase 2 study to evaluate the efficacy and safety of 2 CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM)," *Blood*, Abstract # 825, *American Society of Hematology*, Dec. 6-9, 2003.
- Richardson et al., "A multicenter, single-arm, open-label study to evaluate the efficacy and safety of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma: preliminary results," *10th International Myeloma Workshop*, Apr. 10-14, 2005.
- Richardson et al., "A Phase I study of oral CC5013, an immunomodulatory thalidomide (Thal) derivative, in patients with relapsed and refractory multiple myeloma (MM)," *Blood*, Abstract #3225, Dec. 7-11, 2001, *American Society of Hematology*.
- Richardson et al., "A phase I trial of lenalidomide (REVLIMID®) with bortezomib (VELCADE®) in relapsed and refractory multiple myeloma," *Blood*, Abstract # 365, *American Society of Hematology*, Dec. 10-13, 2005.
- Richardson et al., "Immunomodulatory analogs of thalidomide: an emerging new therapy in myeloma," *Journal of Clinical Oncology*, 2004, 22(16):3212-3214.
- Richardson et al., "Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma," *Blood*, 2002, 100:3063-3067, *American Society of Hematology*.
- Richardson et al., "Novel biological therapies for the treatment of multiple myeloma," *Best Practice & Research Clinical Haematology*, 2005, 18 (4):619-634.
- Rubin et al., "Principles of cancer treatment-1," 2003, 12 ONCO IV 1.
- Schafer et al., "Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs," *Journal of Pharmacology and Experimental Therapeutics*, 2003, 305(3):1222-1232.
- Schey et al., "A phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma," *Journal of Clinical Oncology*, 2004, 22 (16):1-8.
- Schey et al., "A phase I study of an immunomodulatory thalidomide analogue (CC4047) in relapse/refractory multiple myeloma," *International Society for Experimental Hematology*, Abstract #248, 2002.
- Shah et al., 1999, "Synthesis and enantiomeric separation of 2-phthalimidino-glutaric acid analogues: potent inhibitors of tumor metastasis," *J. Med. Chem.* 42:3014-3017.

US 7,465,800 B2

Page 5

- Shaughnessy et al., "Global gene expression analysis shows loss of C-MYC and IL-6 receptor gene mRNA after exposure of myeloma to thalidomide and IMiD," Abstract # 2485, *American Society of Hematology*, Dec. 1-5, 2000.
- Shire et al., "TNF- α inhibitors and rheumatoid arthritis," *Exp. Opin. Ther. Patents*, 1998, 8 (5):531-544.
- Sorbera et al., "CC-5013. Treatment of multiple myeloma. Treatment of Melanoma. Treatment of myelodysplastic syndrome. Angiogenesis inhibitor. TNF- α production inhibitor," *Drugs of the Future*, 2003, 28(5):425-431.
- Streety et al., "An update of the use and outcomes of the new immunomodulatory agent CC-4047 (Actimid) in patients with relapsed/refractory myeloma," Abstract #829, *American Society of Hematology*, Dec. 6-9, 2003.
- Streety et al., "Changes in neutrophil phenotype following the administration of CC-4047 (Actimid) to patients with multiple myeloma," Abstract # 2543, *American Society of Hematology*, Dec. 6-9, 2003.
- Streety et al., "Thalidomide analogue CC-4047 is effective in the treatment of patients with relapsed and refractory multiple myeloma (MM) and induces T-cell activation and IL-12 production," Abstract # 367, *International Multiple Myeloma Workshop*, May 23-27, 2003.
- Teo et al., "A phase I, single-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacokinetic study of CDC-501, a novel immunomodulatory- oncologic agent, in healthy male subjects with a comparison of fed and fasted," *Clinical Pharmacology and Therapeutics*, 2002, 71 (2)93.
- Teo et al., "Chiral inversion of the second generation IMiD™ CC-4047 (ACTIMID™) in human plasma and phosphate-buffered saline," *Chirality*, 2003, 15:348-351.
- Thertulien et al., "Hybrid MEL/DT Pace autotransplant regimen for Multiple Myeloma (MM)- safety and efficacy data in pilot study of 15 patients," *Blood*, Abstract # 2869, *American Society of Hematology*, Dec. 7-11, 2001.
- Tohny et al., "A phase I study of oral CC-5013 (lenalidomide, Revlimid™), a thalidomide derivative in patients with refractory metastatic cancer," *Clinical Prostate Cancer*, 2004, 2:241-243.
- Tricot et al., "Angiochemotherapy (ACT) for multiple myeloma (MM) with DT-Pace results in a high response rate, but in contrast to tandem transplants with melphalan does not affect durable disease control," *Blood*, Abstract # 3531, *American Society of Hematology*, Dec. 7-11, 2001.
- Tsenova et al., "Use of IMiD3, a thalidomide analog, as an adjunct to therapy for experimental tuberculous meningitis," *Antimicrobial Agents and Chemotherapy*, 2002, 46 (6):1887-1895.
- Weber et al., "A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma," Abstract # PO.738, *International Multiple Myeloma Workshop*, Apr. 10-14, 2005.
- Weber, "Lenalidomide (CC-5013), Revlimid™ and other ImiDs," Abstract # PL5.02, *International Multiple Myeloma Workshop*, Apr. 10-14, 2005.
- Ye et al., "Novel IMiD drugs enhance expansion and regulate differentiation of human cord blood CD34+ cells with cytokines," *Blood*, Abstract #4099, *American Society of Hematology*, Dec. 6-10, 2002.
- Zangari et al., "Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDCT)," *American Society of Hematology*, Abstract #3226, 2001.
- Zangari et al., "Revimid 25 mg (REV 25)×20 versus 50 mg (REV 50)×10 q 28 days with bridging of 5 mg×10 versus 10 mg×5 as post-transplant salvage therapy for multiple myeloma (MM)," *Blood*, Abstract # 1642, *American Society of Hematology*, Dec. 6-9, 2003.
- Zangari et al., "Risk factors for deep vein thrombosis (DVT) in a large group of myeloma patients (Pts) treated with thalidomide (Thal): The Arkansas Experience," *Blood*, Abstract # 681, *American Society of Hematology*, Dec. 7-11, 2001.
- Zeldis et al., "Potential new therapeutics for Waldenström's macroglobulinemia," *Seminars in Oncology*, 2003, 30 (2):275-281.
- Zeldis et al., "Update on the evolution of the IMiD™," *International Society for Biological Therapy of Cancer*, Oral Abstract, 2003.
- Zhang et al., "CC-5079, a novel microtubule and TNF- α inhibitor with anti-angiogenic and antimetastasis activity," Abstract # B012, *International Conference on Molecular Targets and Cancer Therapeutics*, Nov. 17-21, 2003.
- U.S. Appl. No. 60/499,723, filed Sep. 4, 2003, Jaworsky.
- U.S. Appl. No. 10/693,794, filed Oct. 23, 2003, Zeldis.
- DiMartino et al., 1997, "Preparation and physical characterization of forms II and III of paracetamol," *J. Thermal Analysis* 48:447-458.
- Jonsson, 1972, "Chemical structure and teratogenic properties. 3. A review of available data on structure-activity relationships and mechanism of action of thalidomide analogues," *Acta. Pharm. Suec.* 9(6):521-542.
- Wilen et al., 1977, "Strategies in optical resolutions," *Tetrahedron* 33:2725-2736.
- Wilen, 1972, *Tables of Resolving Agents and Optical Resolutions*, Eliel, ed., U. Notre Dame Press, Notre Dame, IN pp. 268.
- Wolff, ed., 1995, *I Burger's Medicinal Chemistry and Drug Discovery*, 5th ed., pp. 172-178 and 949-982.
- Corral et al., 1999, "Immunomodulation by thalidomide and thalidomide analogs," *Ann. Rheum. Dis.* 58(Supp. 1):1107-1113.
- Grant, 1999, "Theory and Origin of Polymorphism," in *Polymorphism in Pharmaceutical Solids*, Minneapolis, MN, Ch. 1, pp. 1-10.
- He, W., et al., 1993, 206th American Chemical Society, Chicago, IL; Med. Chem., paper 216.
- Lentzsch et al., 2002, "S-3-Amino-phthalimido-glutarimide inhibits angiogenesis and growth of B-cell neoplasias in mice," *Cancer Research* 62:2300-2305.
- Muller et al., 1999, "Amino-substituted thalidomide analogs: Potent inhibitors of TNF- α production," *Bioorg. Med. Chem. Lett.* 9:1625-1630.
- Muller et al., 1998, "Thalidomide analogs and PDE4 inhibition," *Bioorg. Med. Chem. Lett.* 8:2669-2674.
- Muller et al., 1996, "Structural modifications of thalidomide produce analogs with enhanced tumor necrosis factor inhibitory activity," *J. Med. Chem.* 39:3238-3240.

* cited by examiner

U.S. Patent

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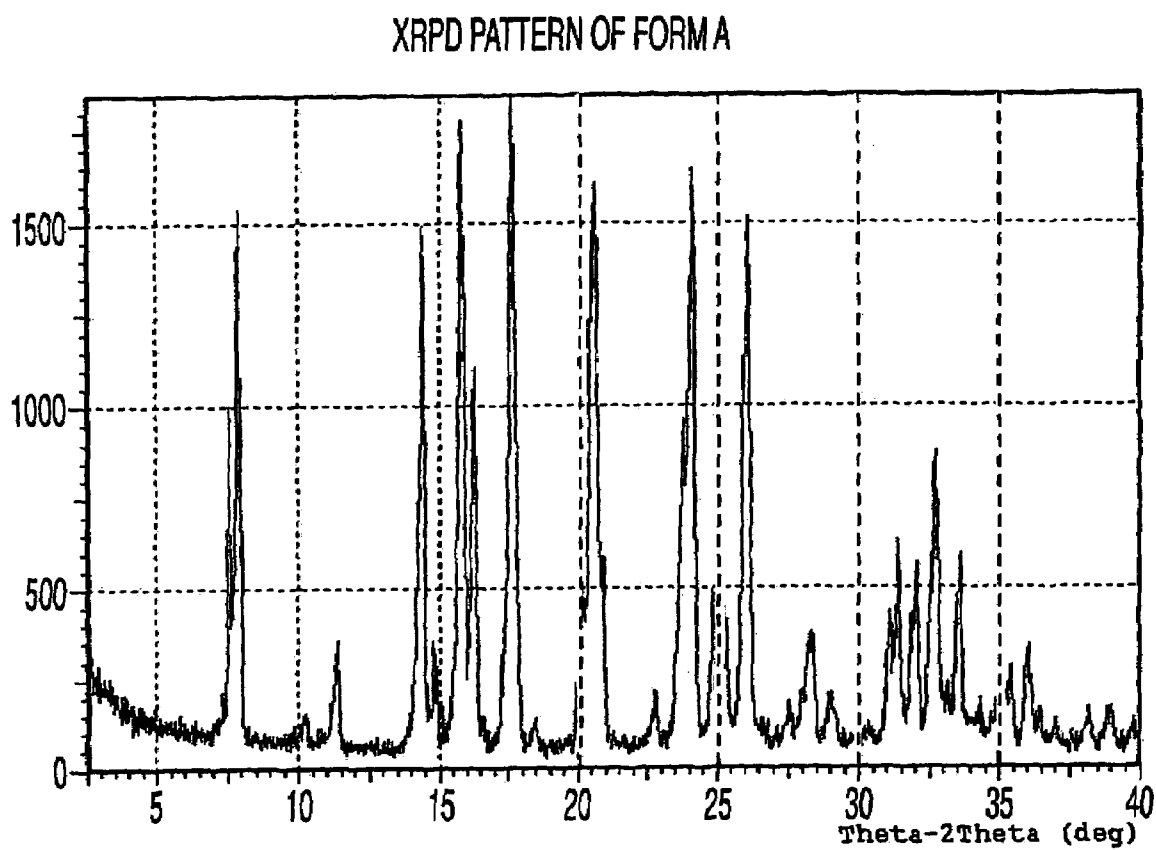


Fig. 1

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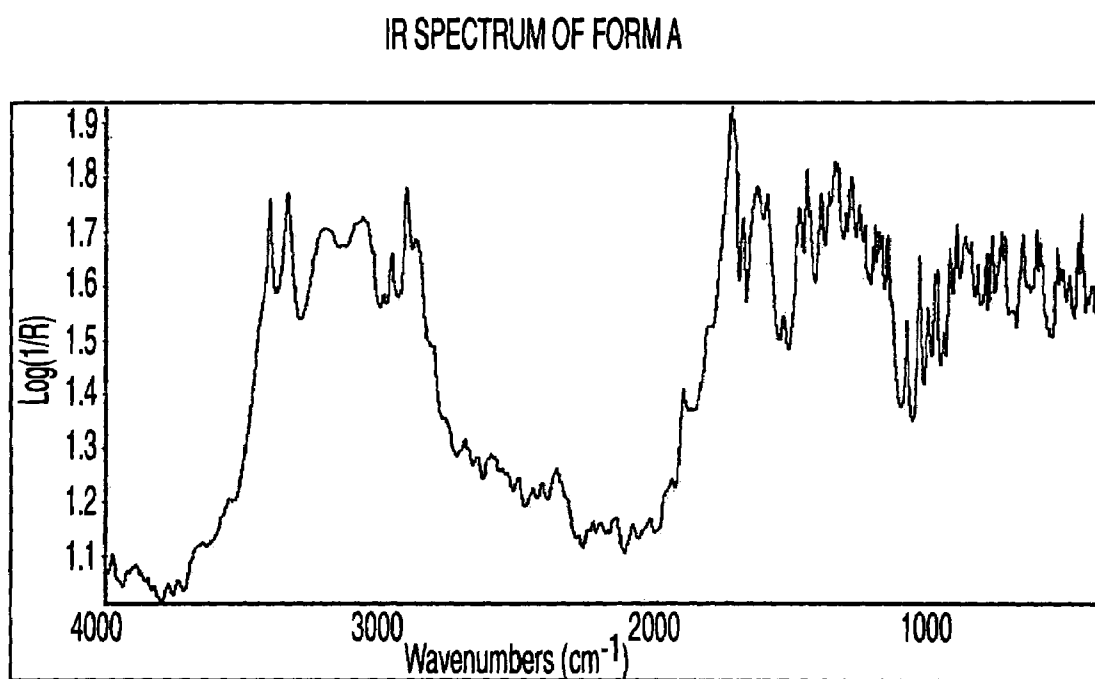


Fig. 2

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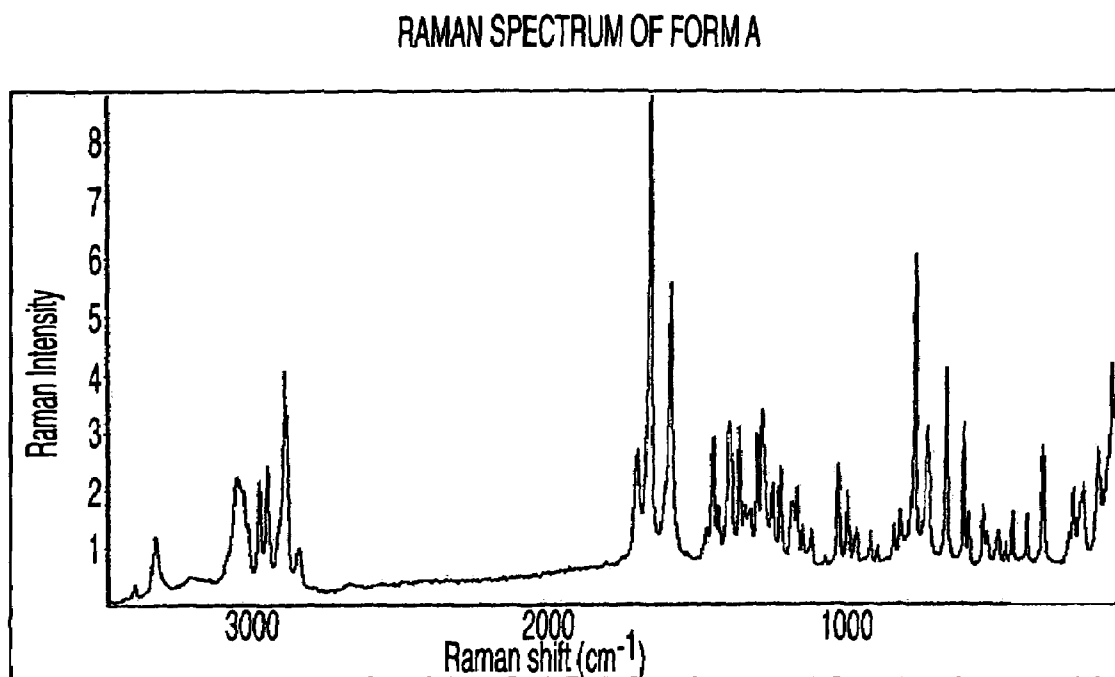


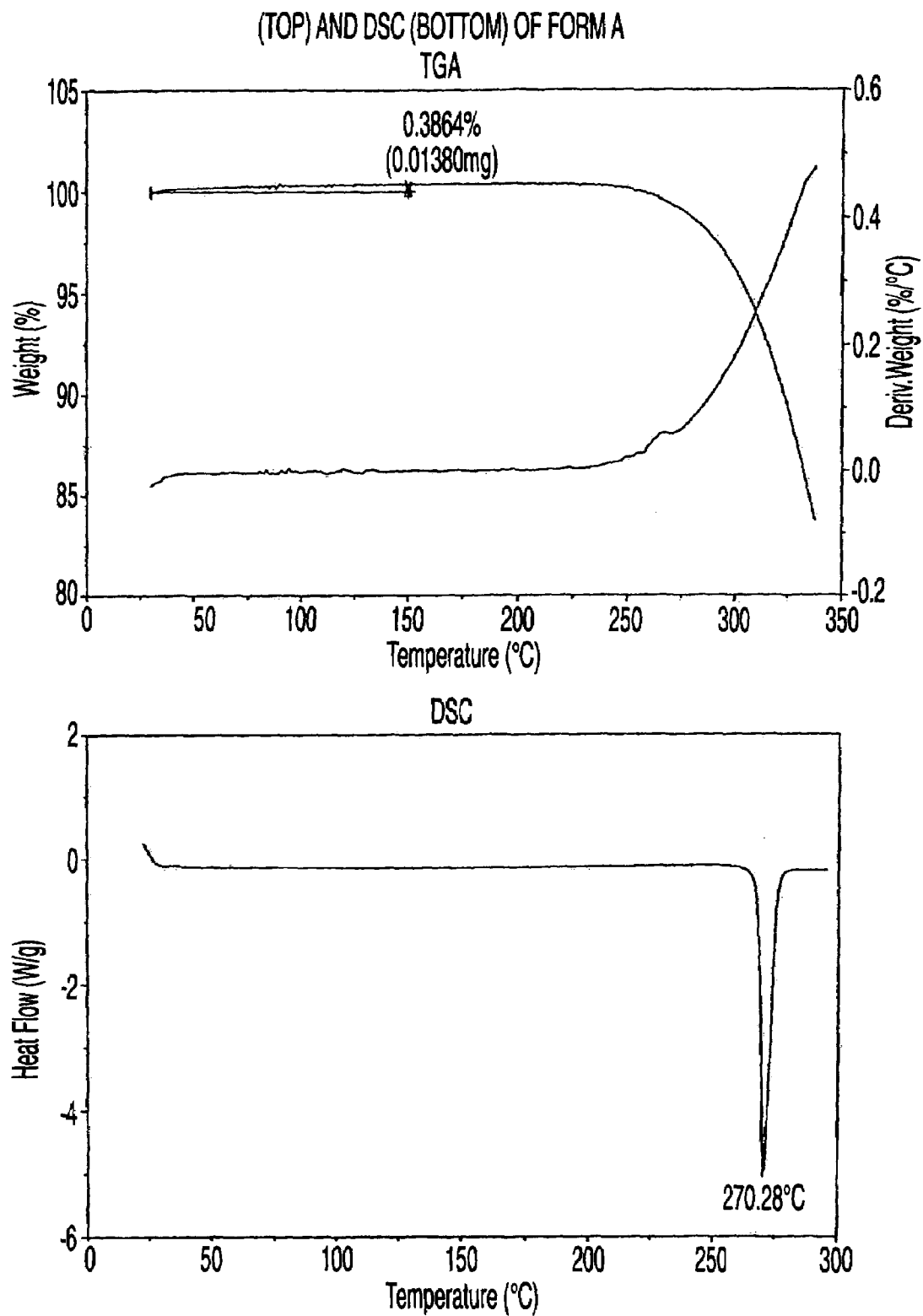
Fig. 3

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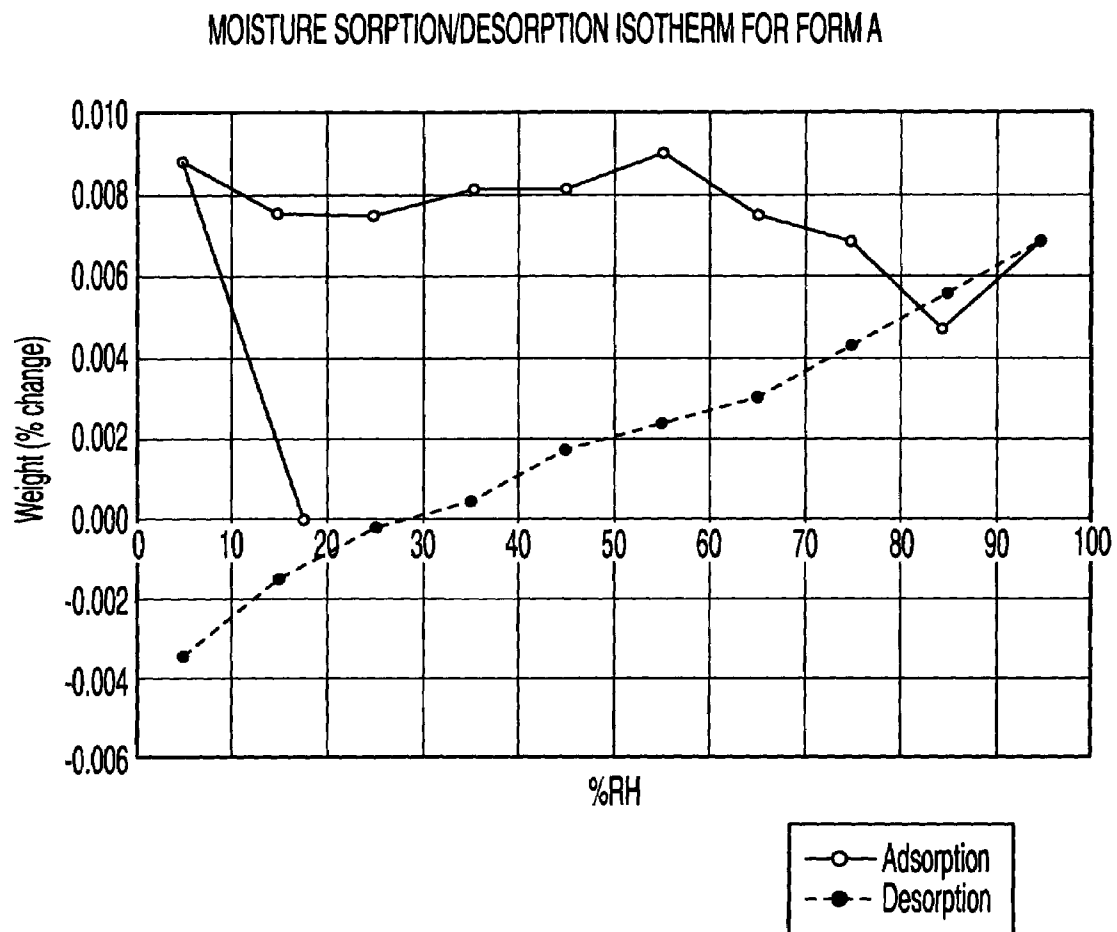
*Fig. 4*

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*Fig. 5*

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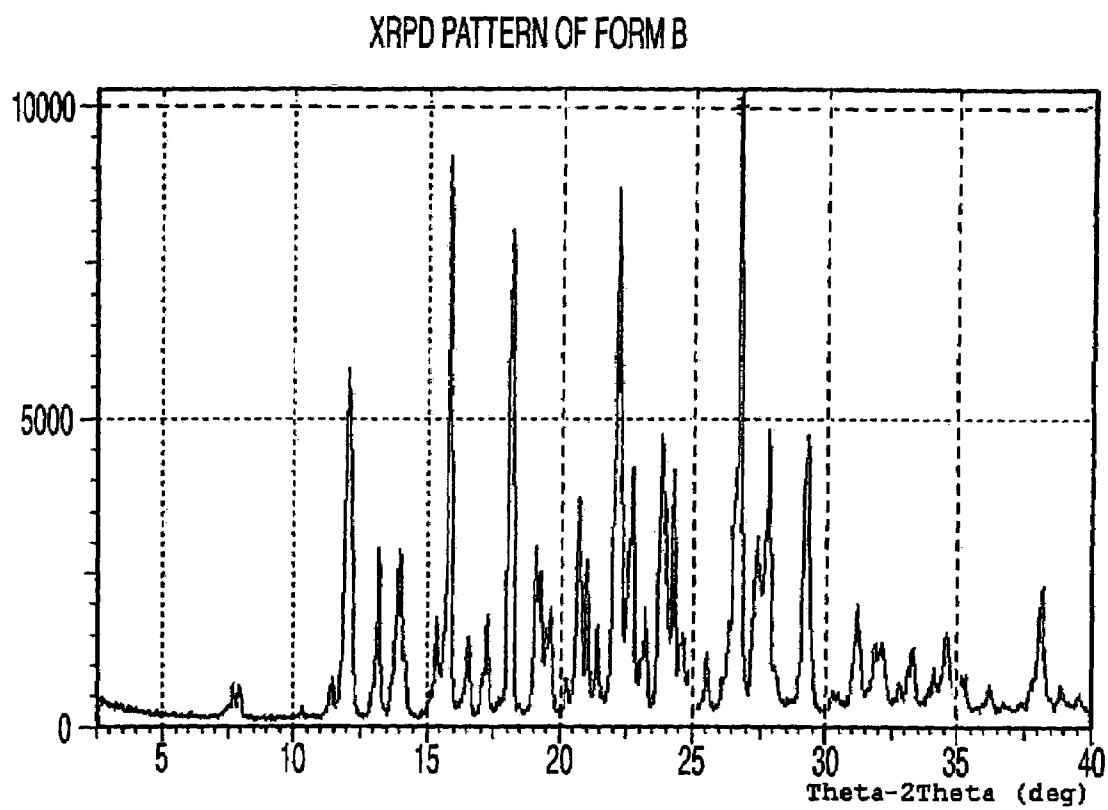


Fig. 6

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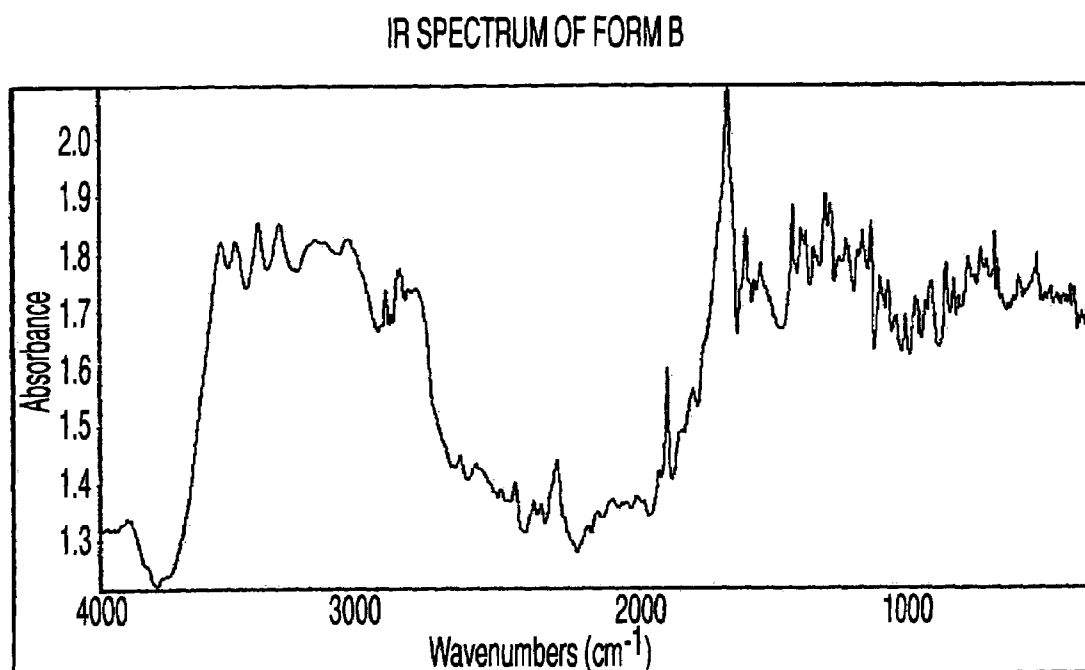


Fig. 7

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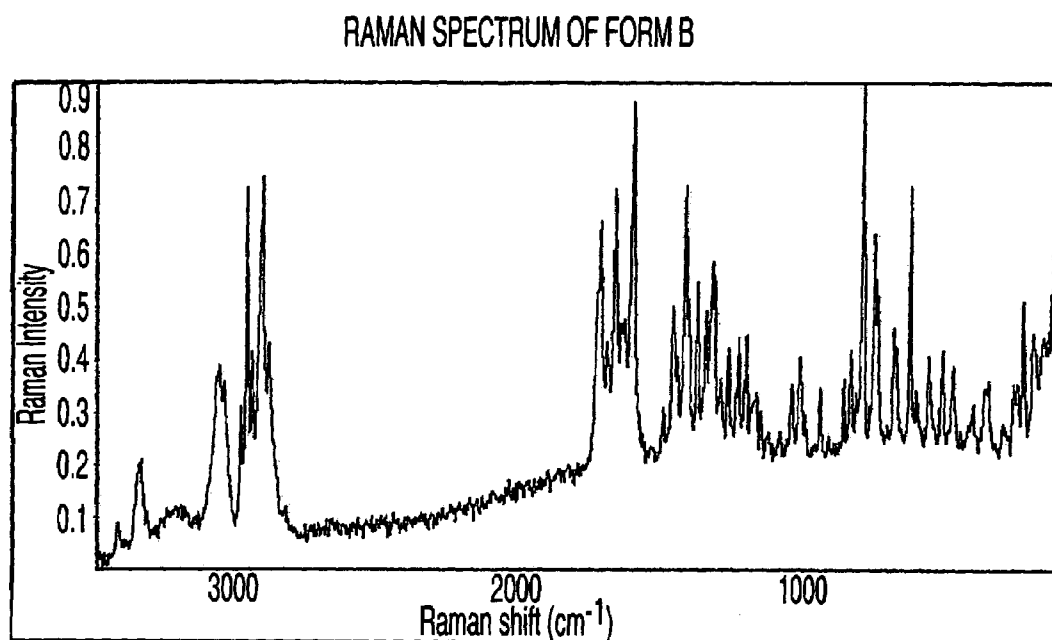


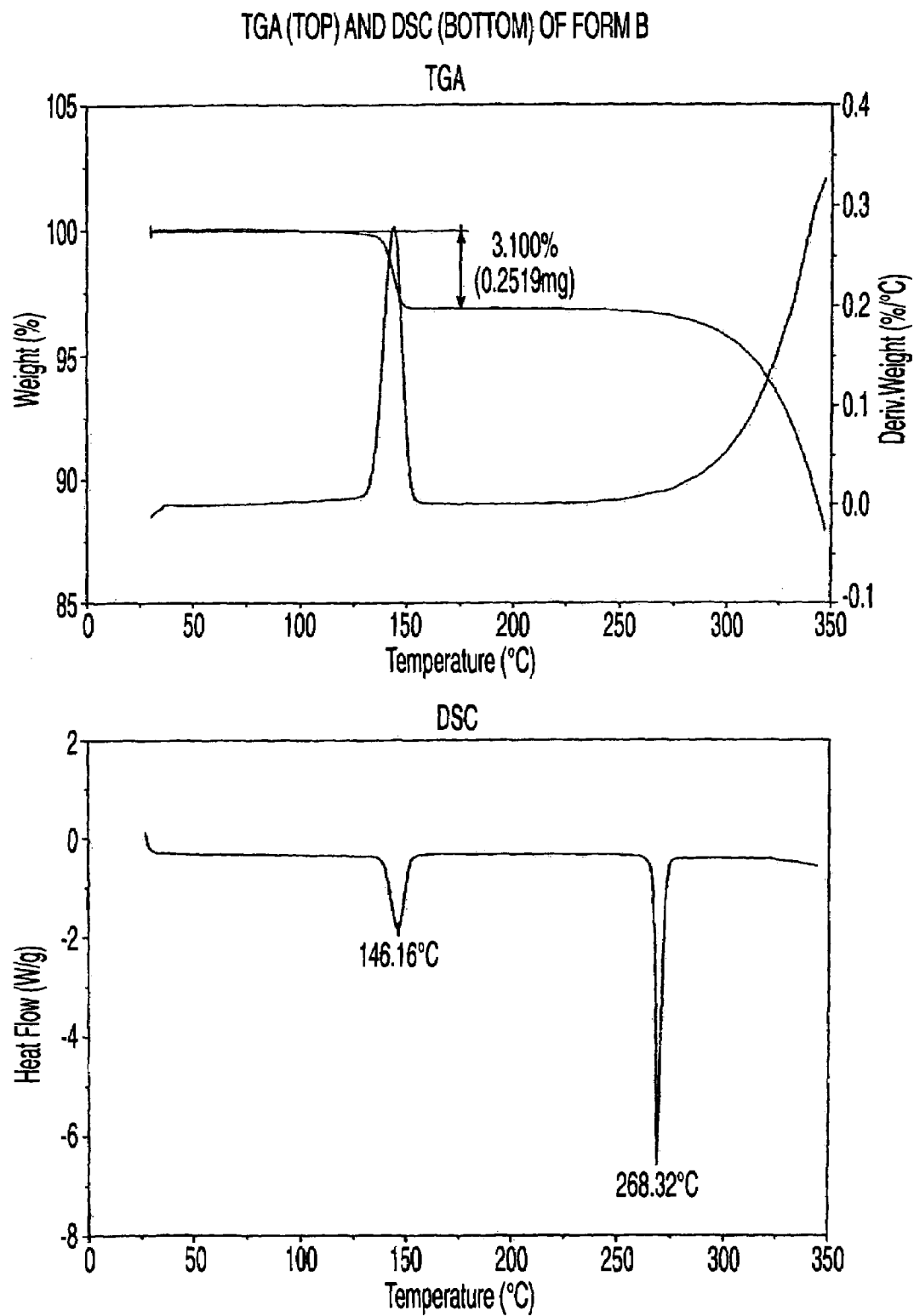
Fig. 8

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*Fig. 9*

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TG-IR RESULTS FOR FORM B

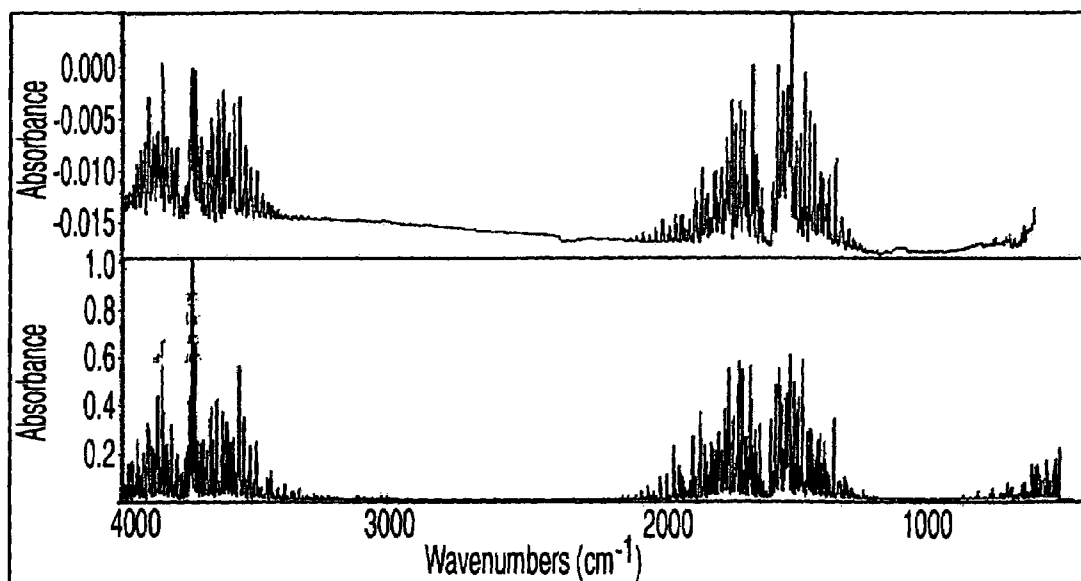
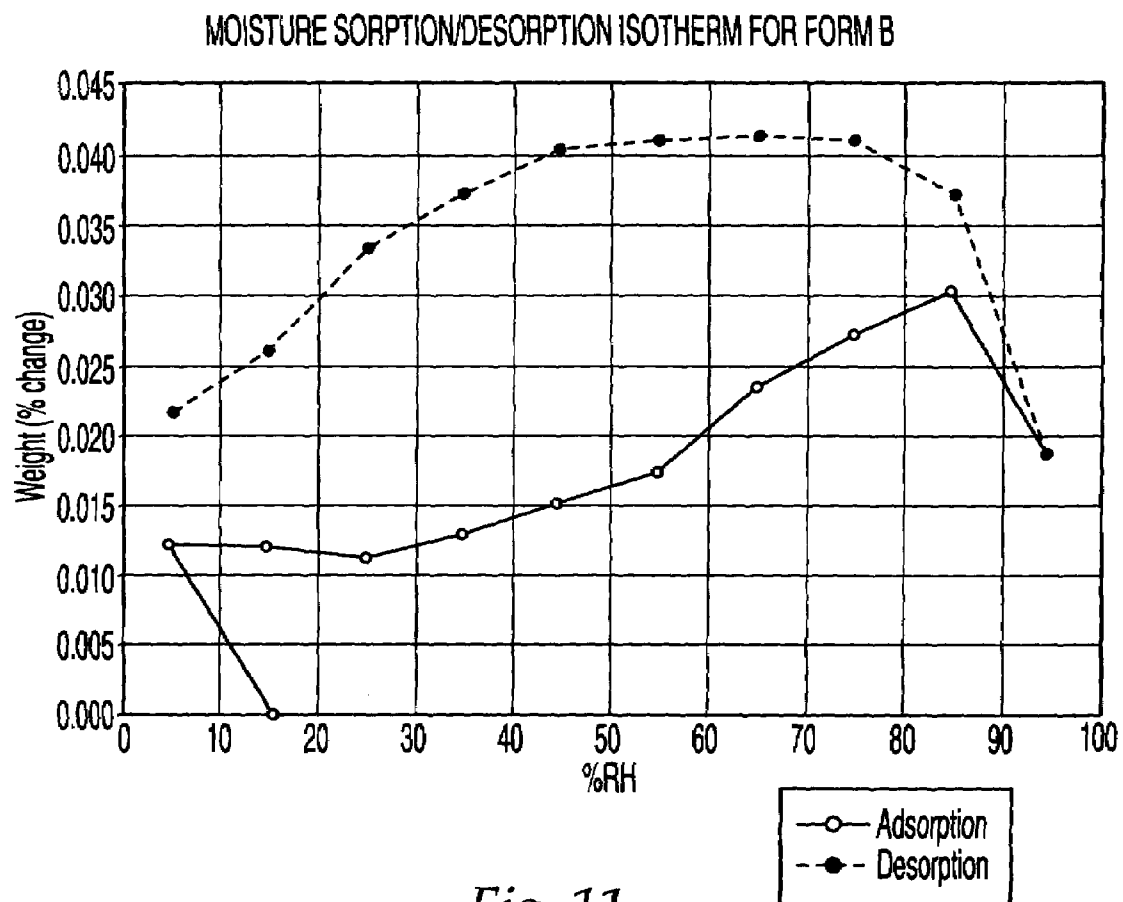


Fig. 10



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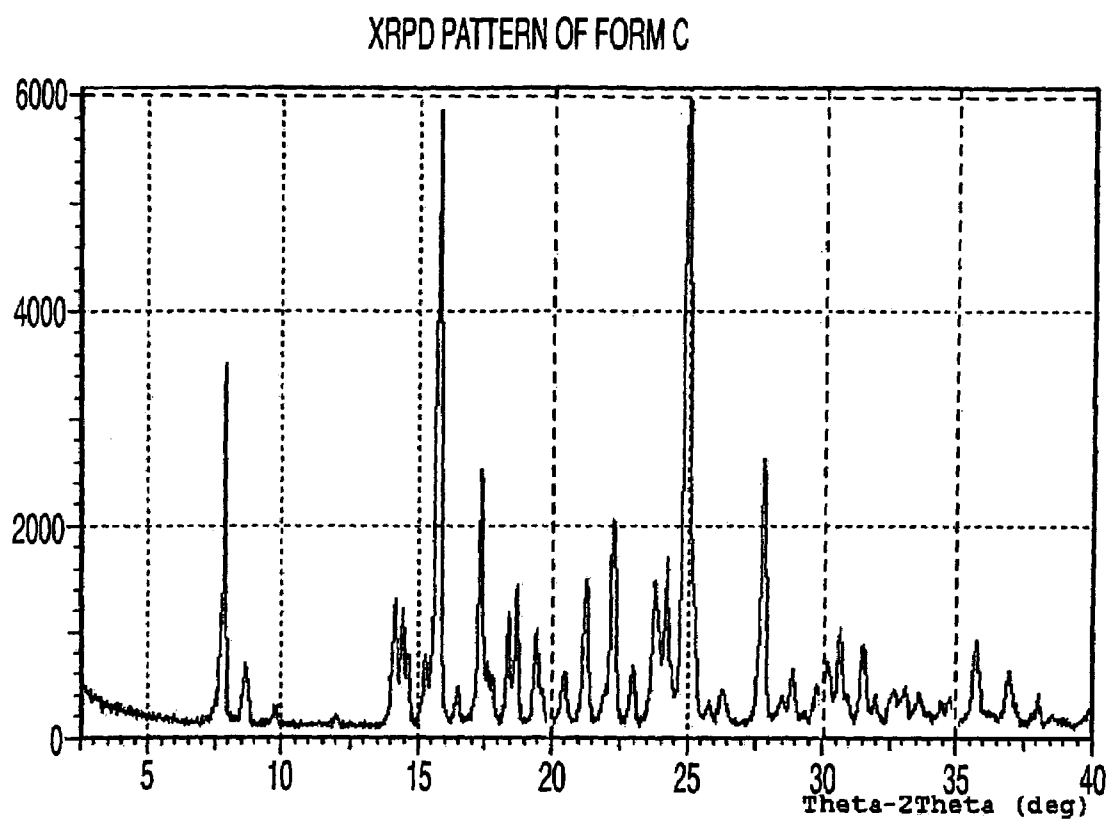


Fig. 12

IR SPECTRUM OF FORM C

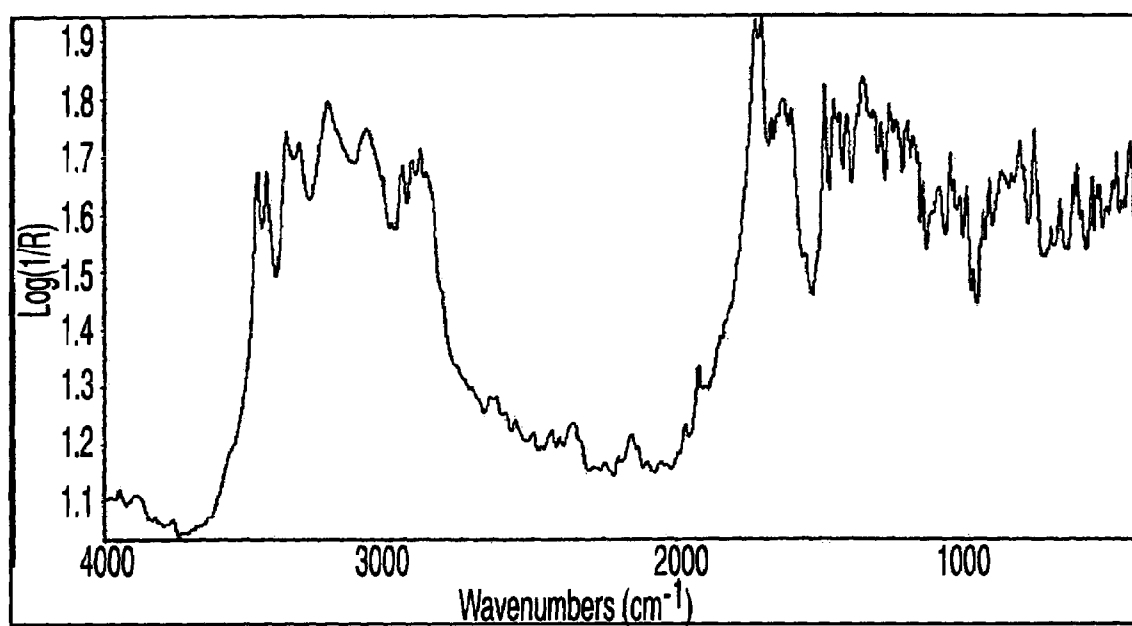


Fig. 13

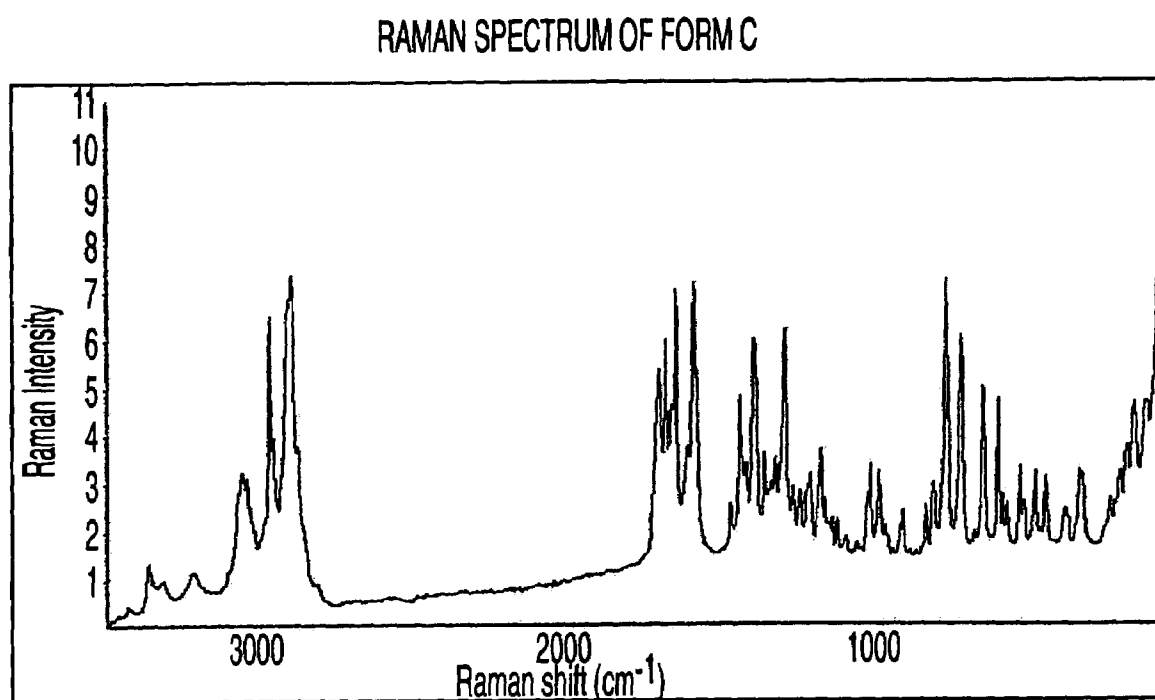


Fig. 14

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TGA (TOP) AND DSC (BOTTOM) OF FORM C

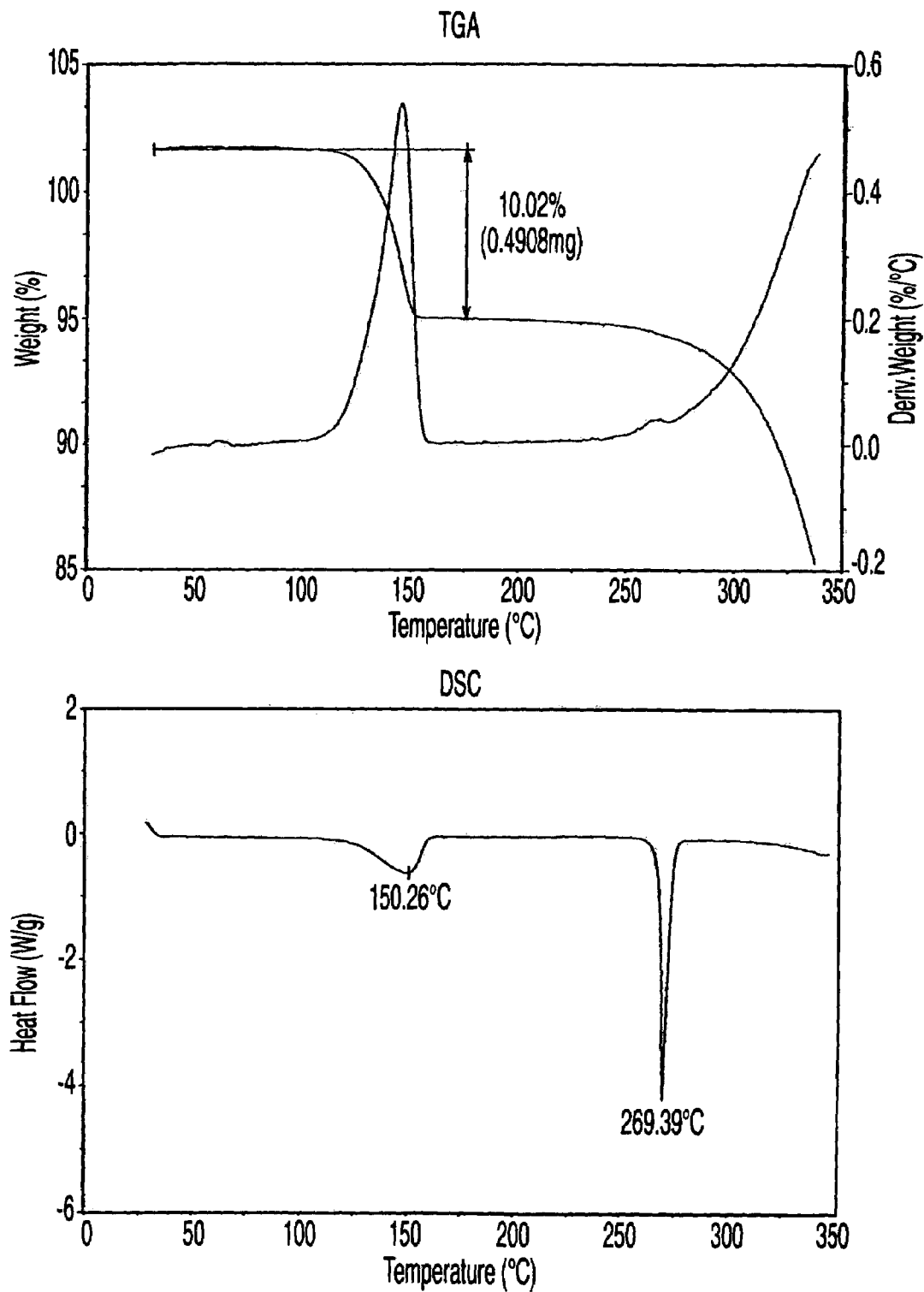


Fig. 15

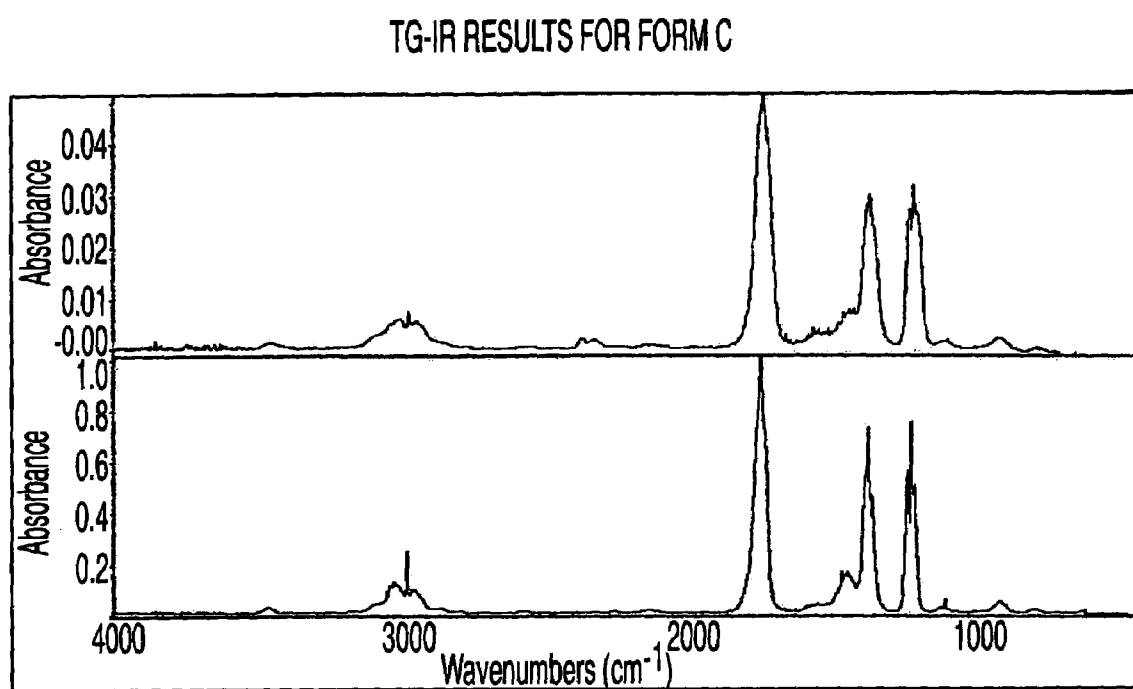


Fig. 16

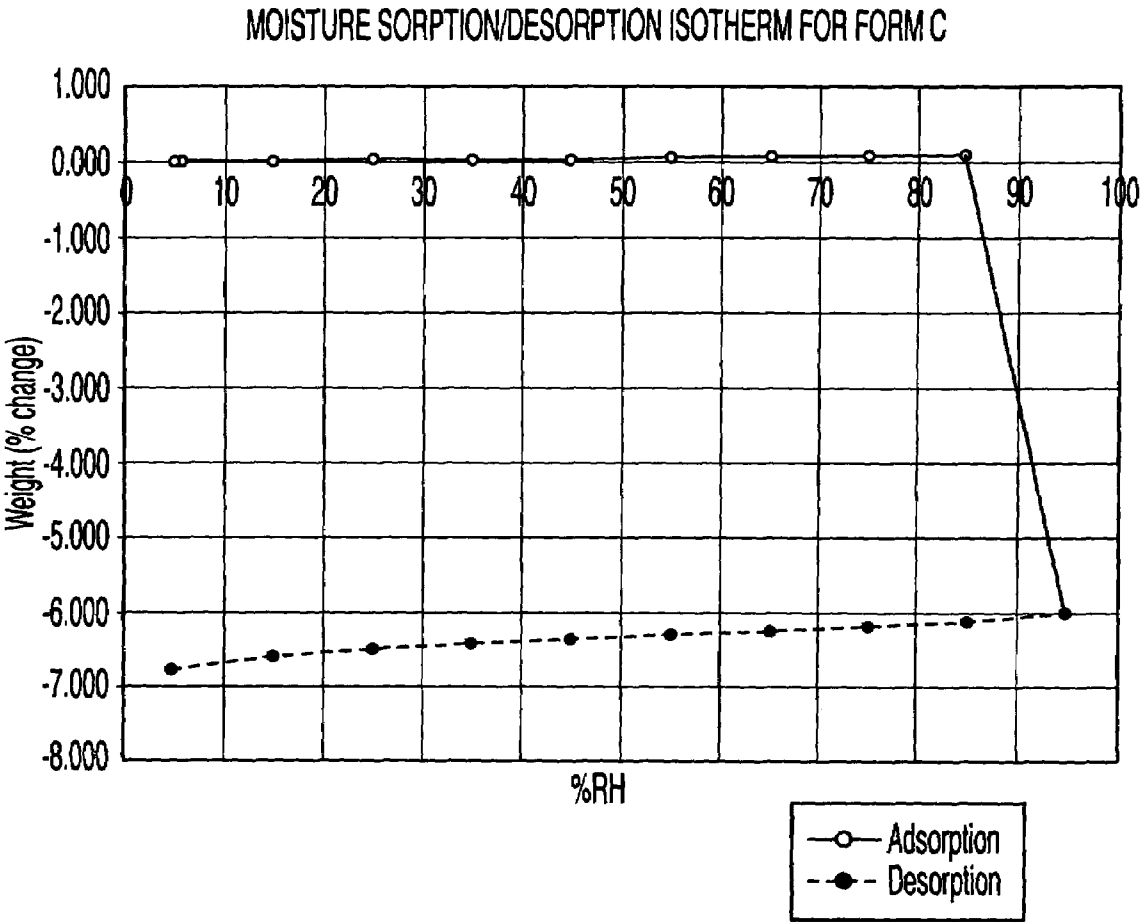


Fig. 17

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XRPD PATTERN OF FORM D

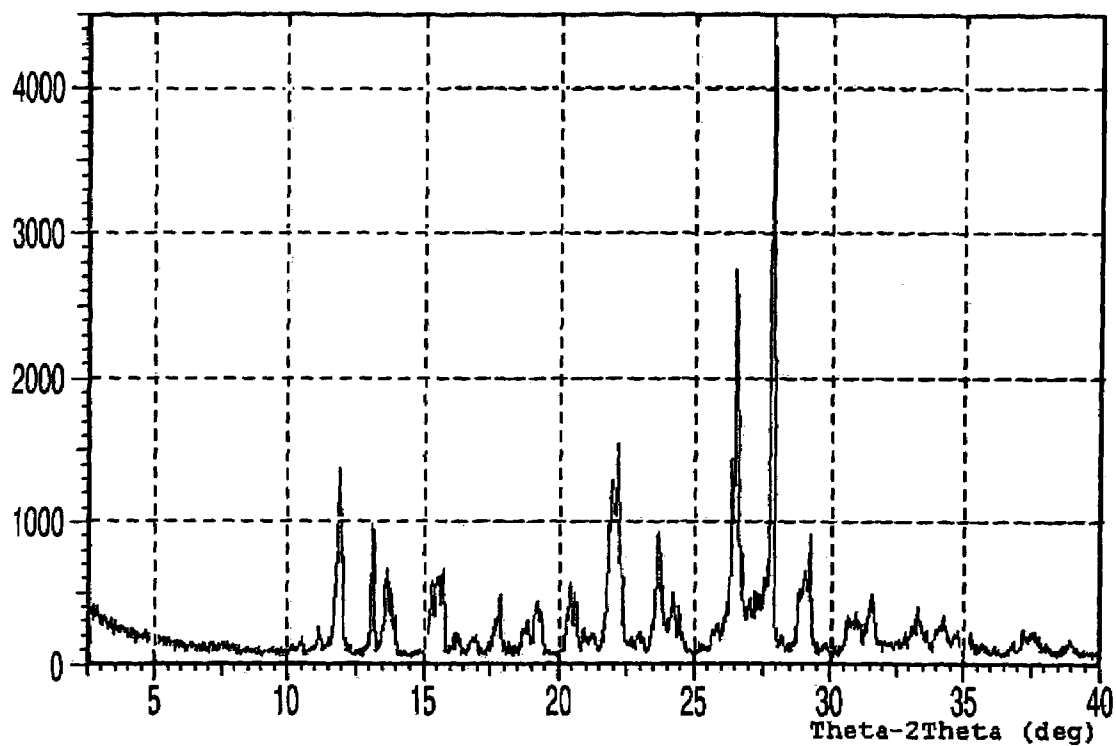


Fig. 18

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IR SPECTRUM OF FORM D

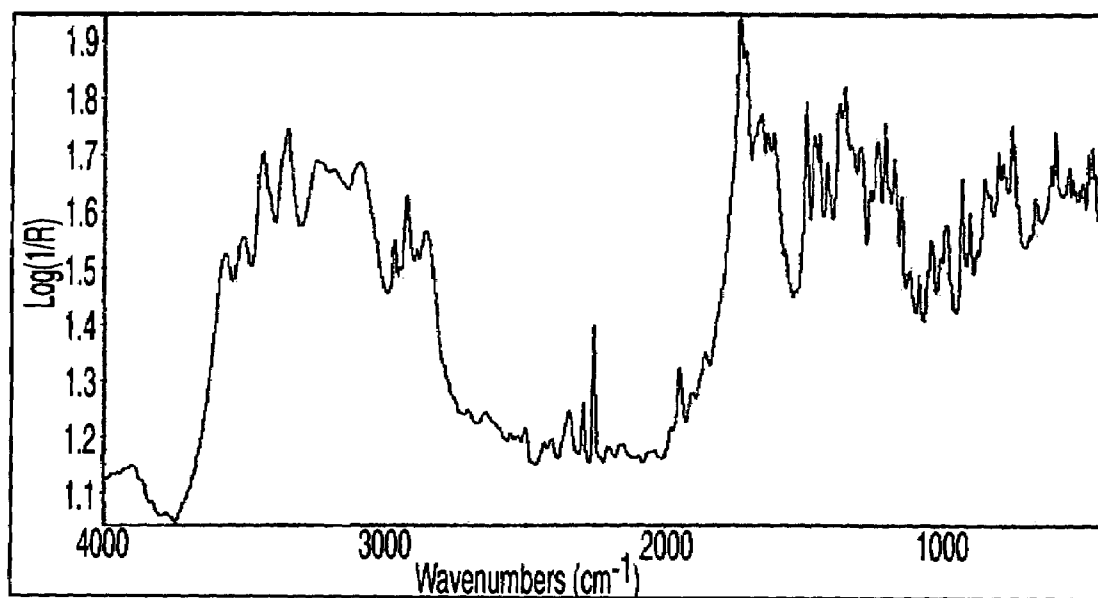


Fig. 19

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RAMAN SPECTRUM OF FORM D

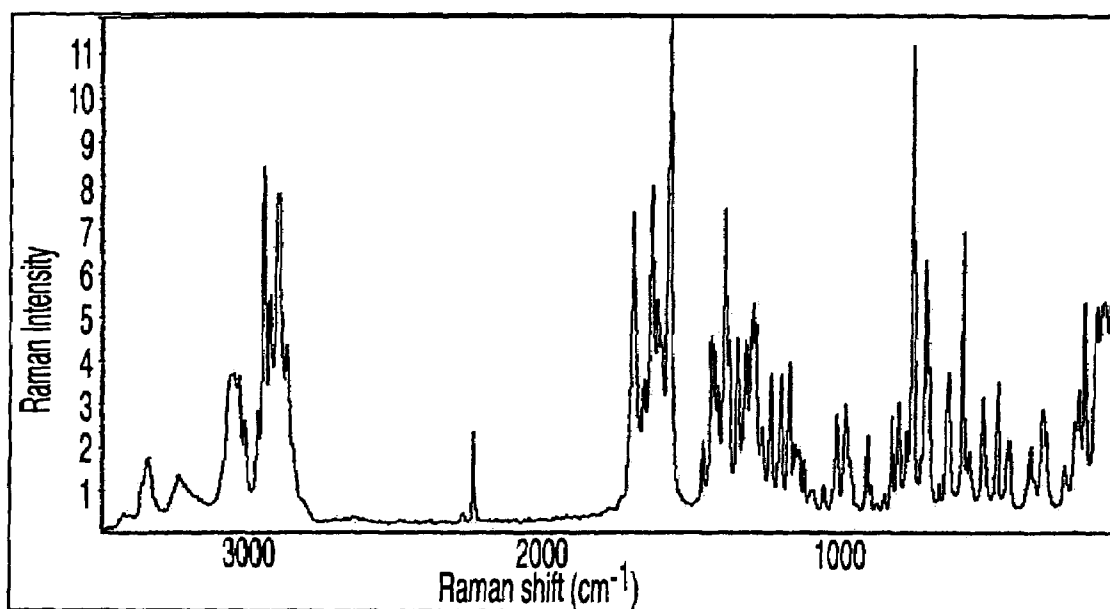


Fig. 20

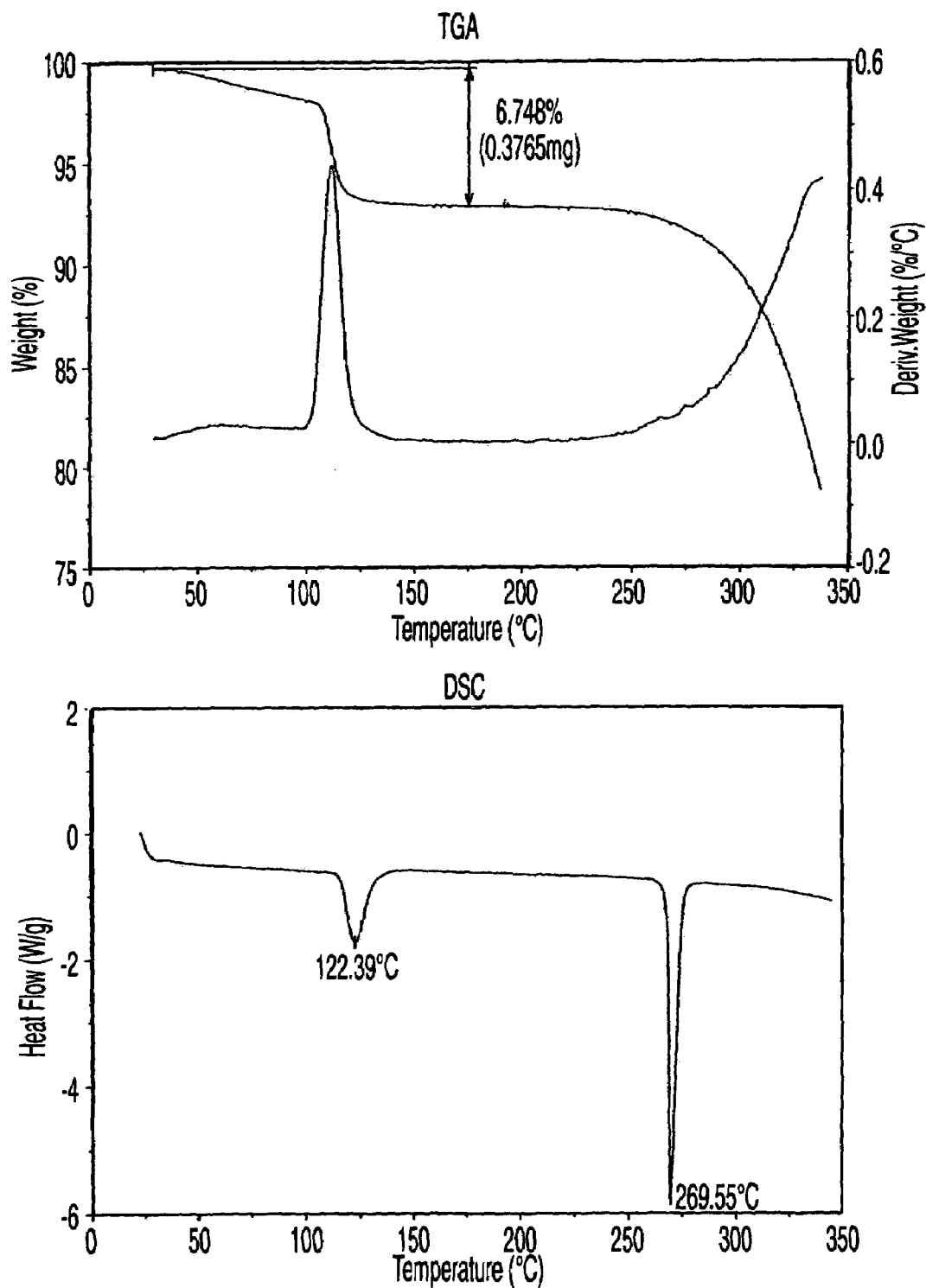
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TGA (TOP) AND DSC (BOTTOM) OF FORM D

*Fig. 21*

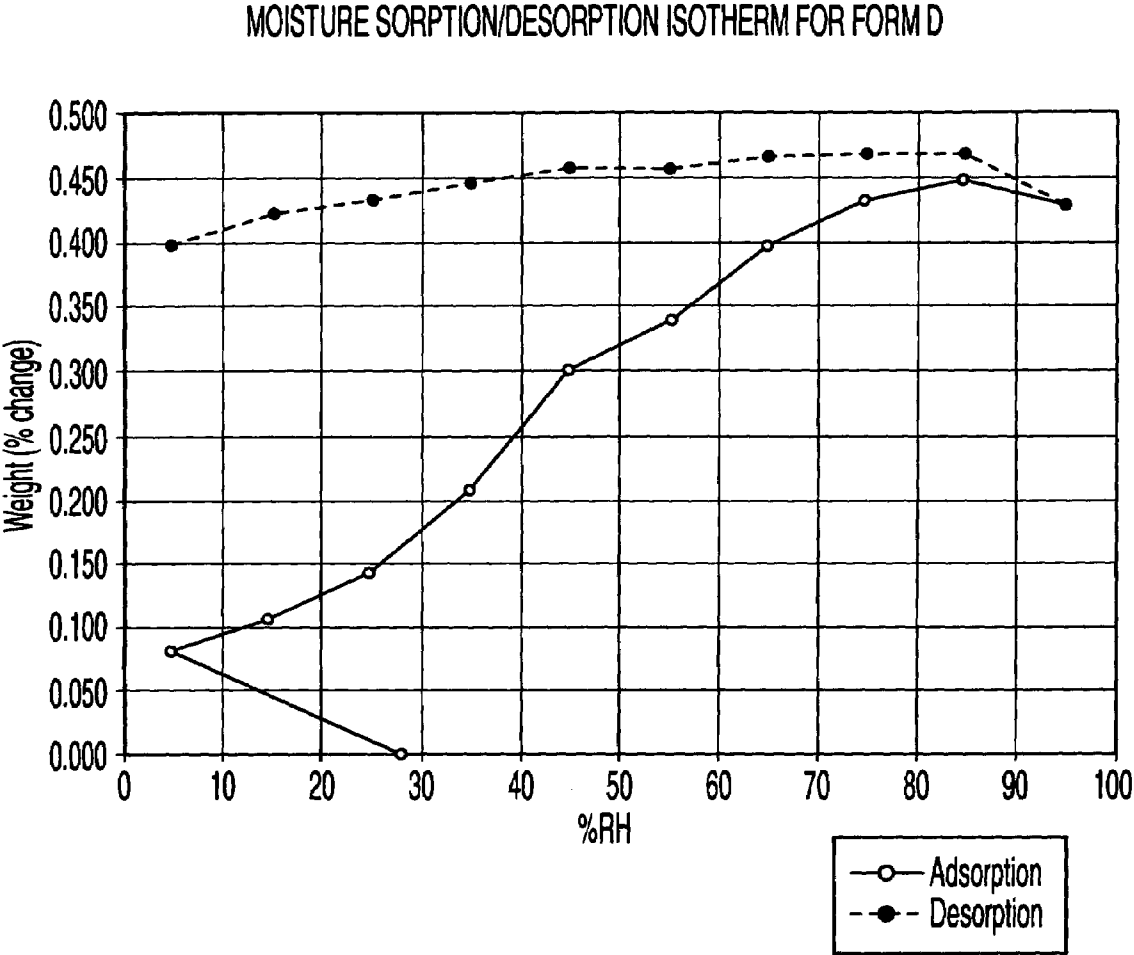


Fig. 22

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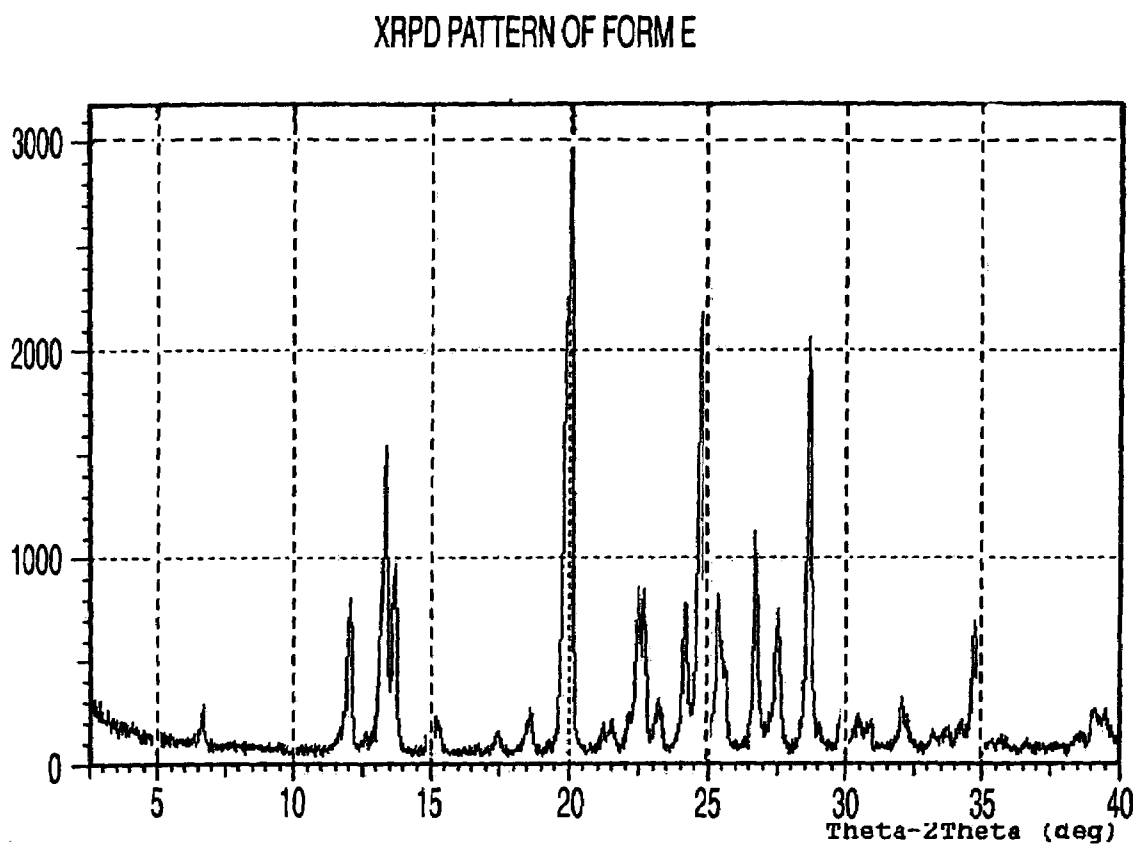
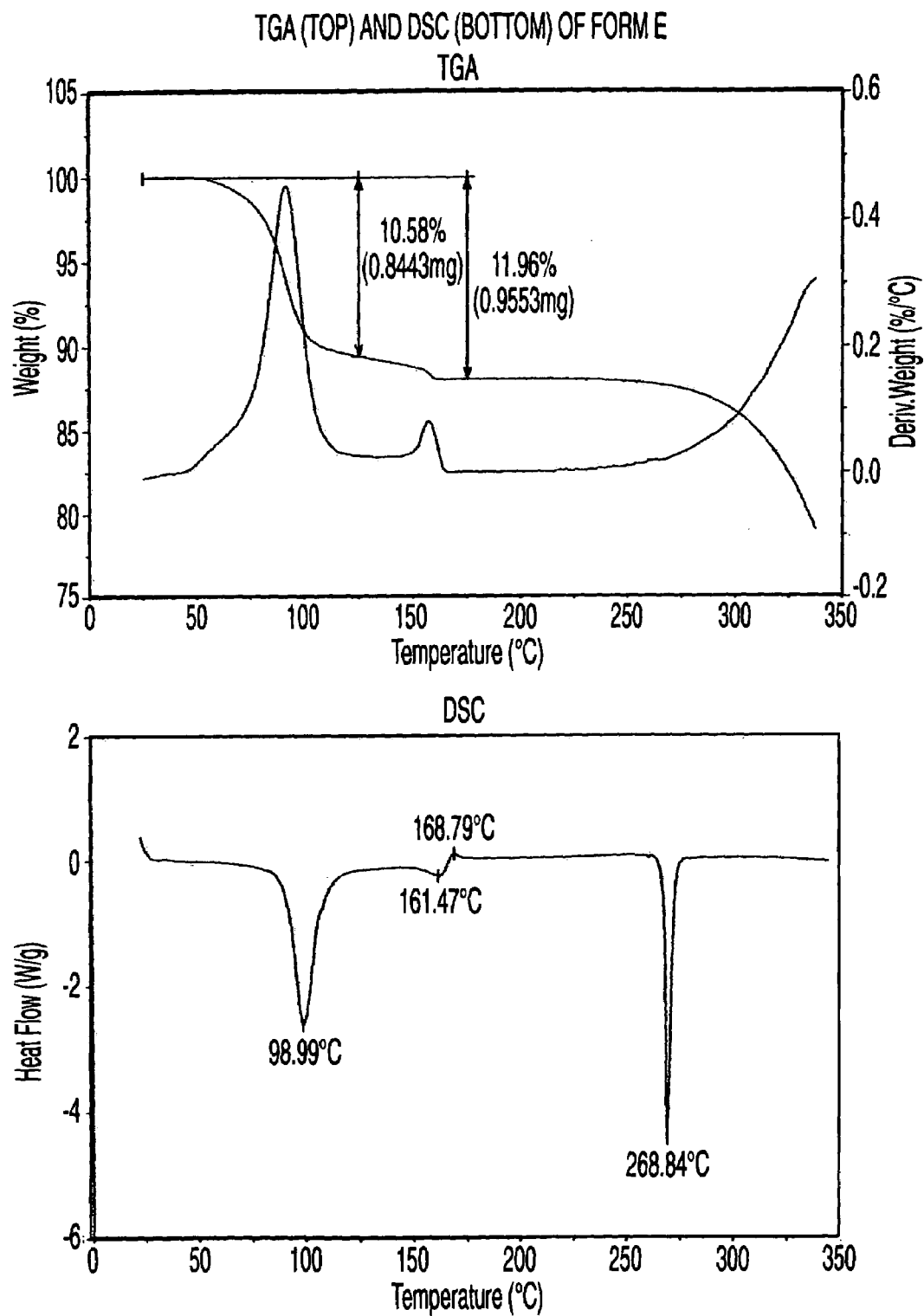
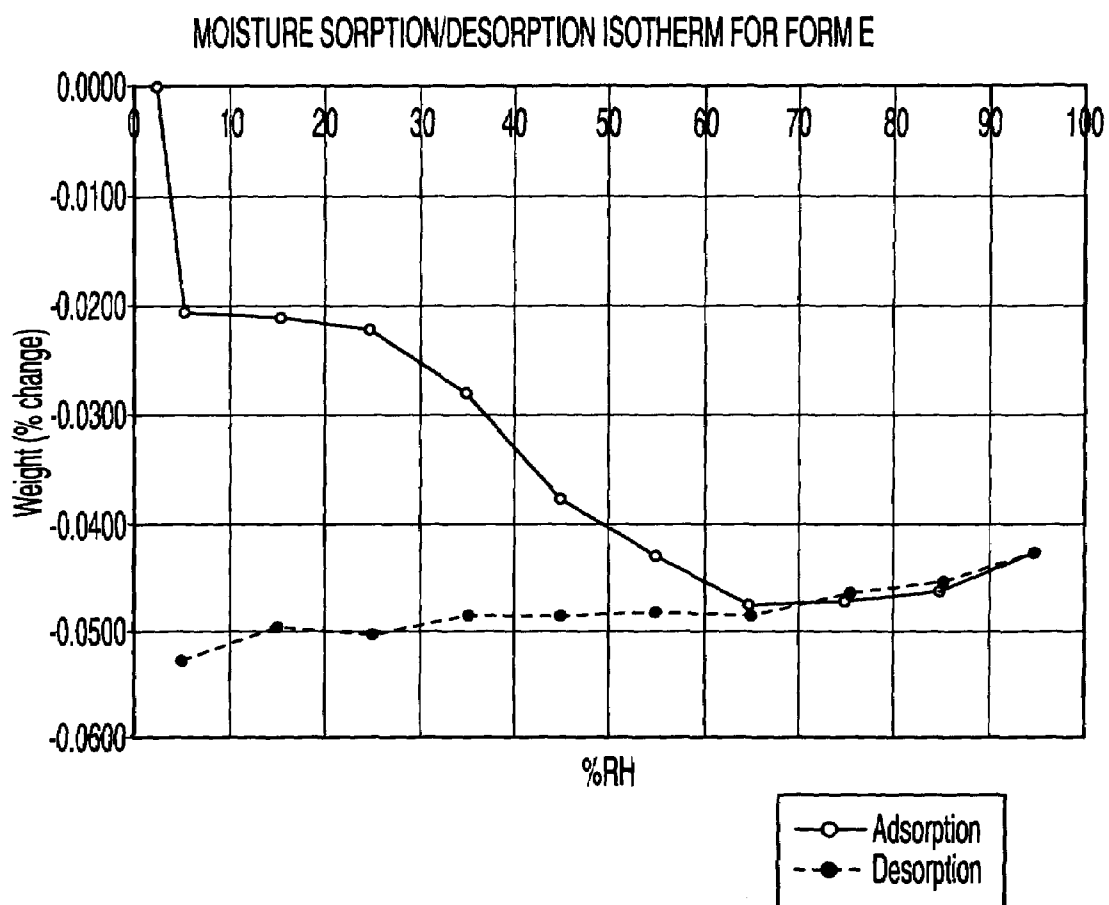


Fig. 23

*Fig. 24*

*Fig. 25*

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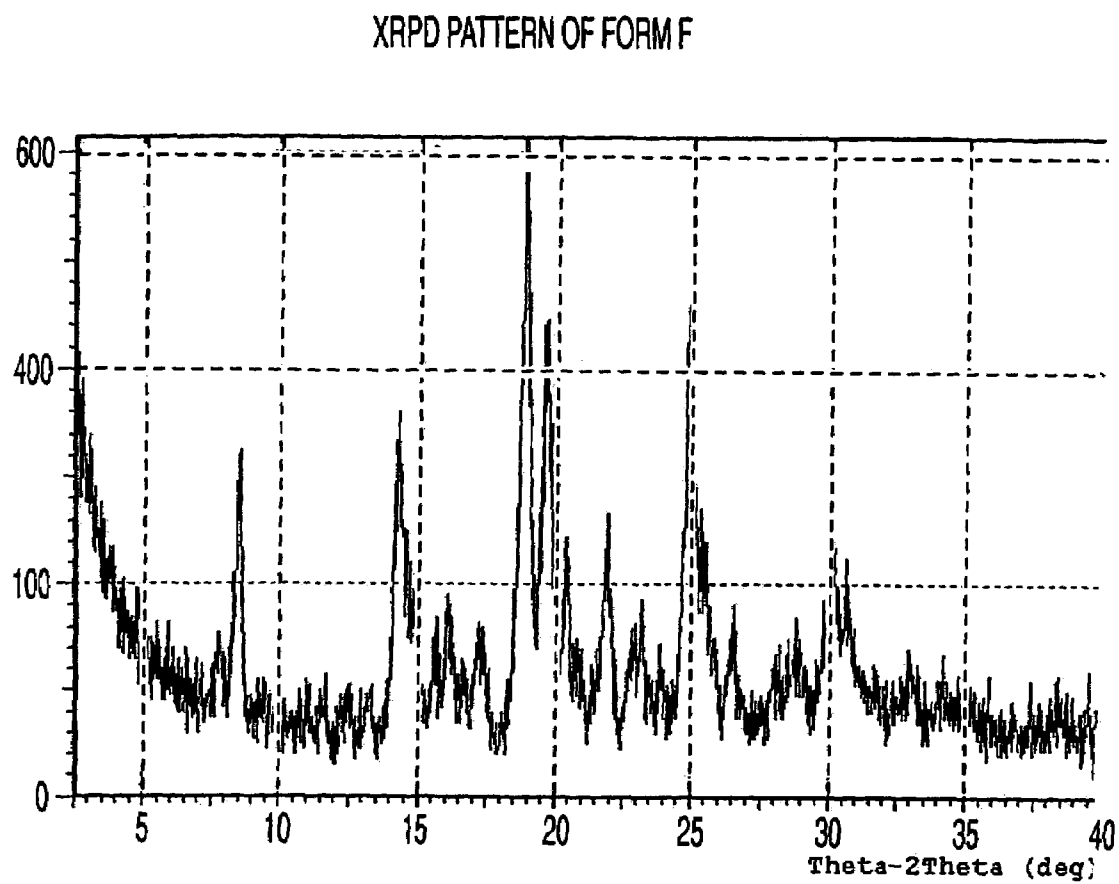


Fig. 26

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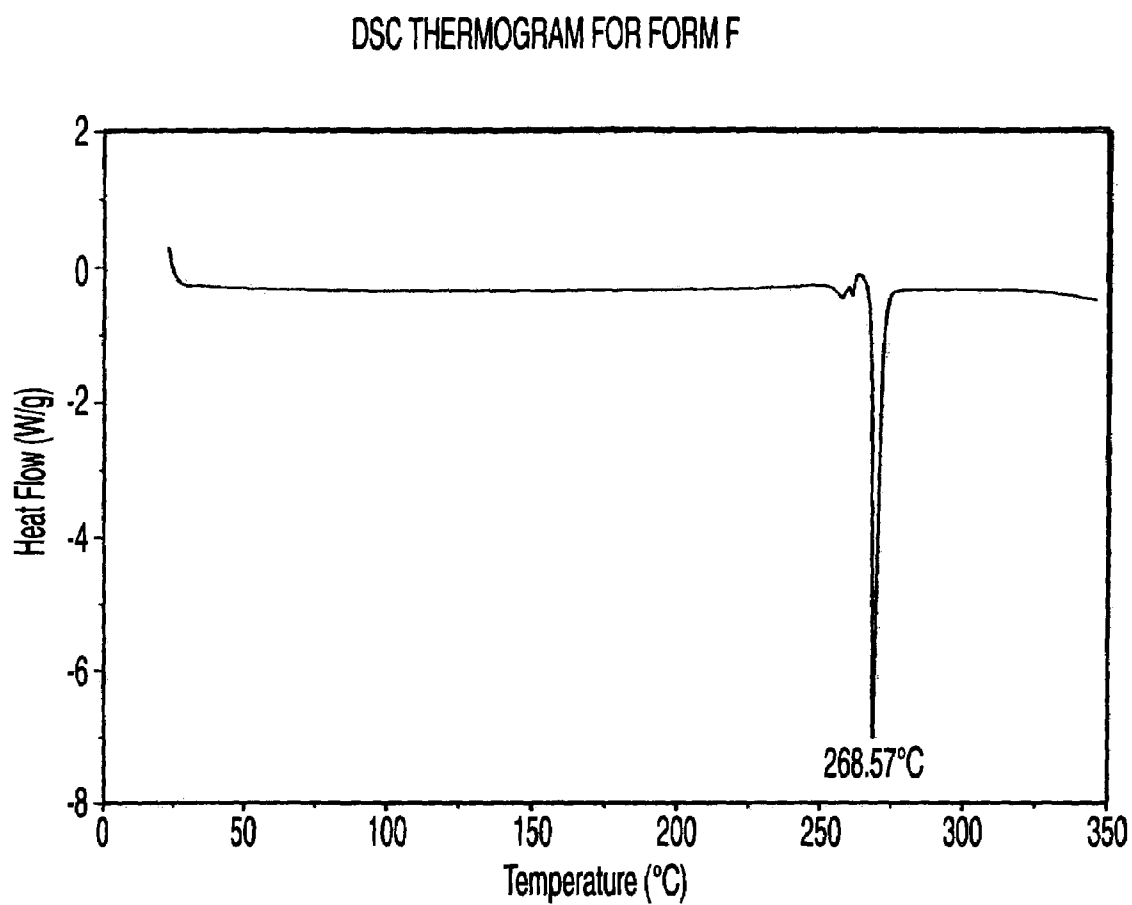


Fig. 27

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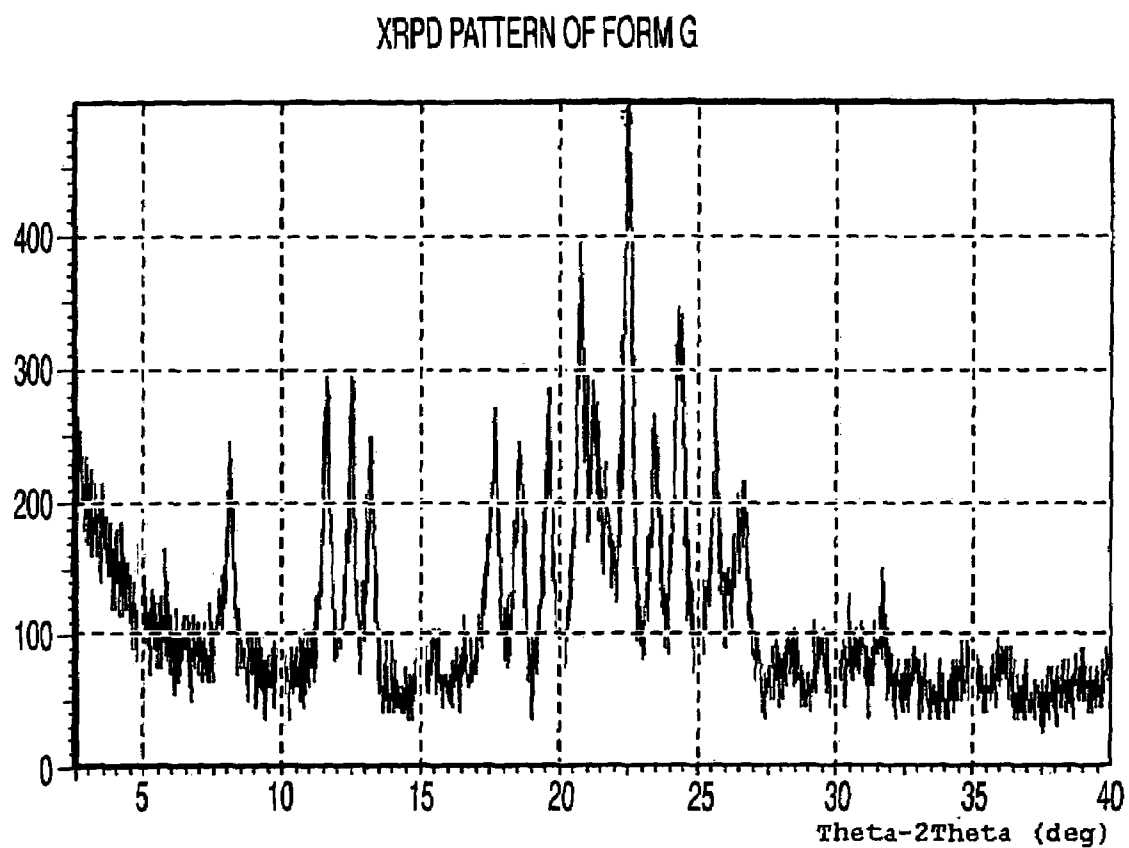


Fig. 28

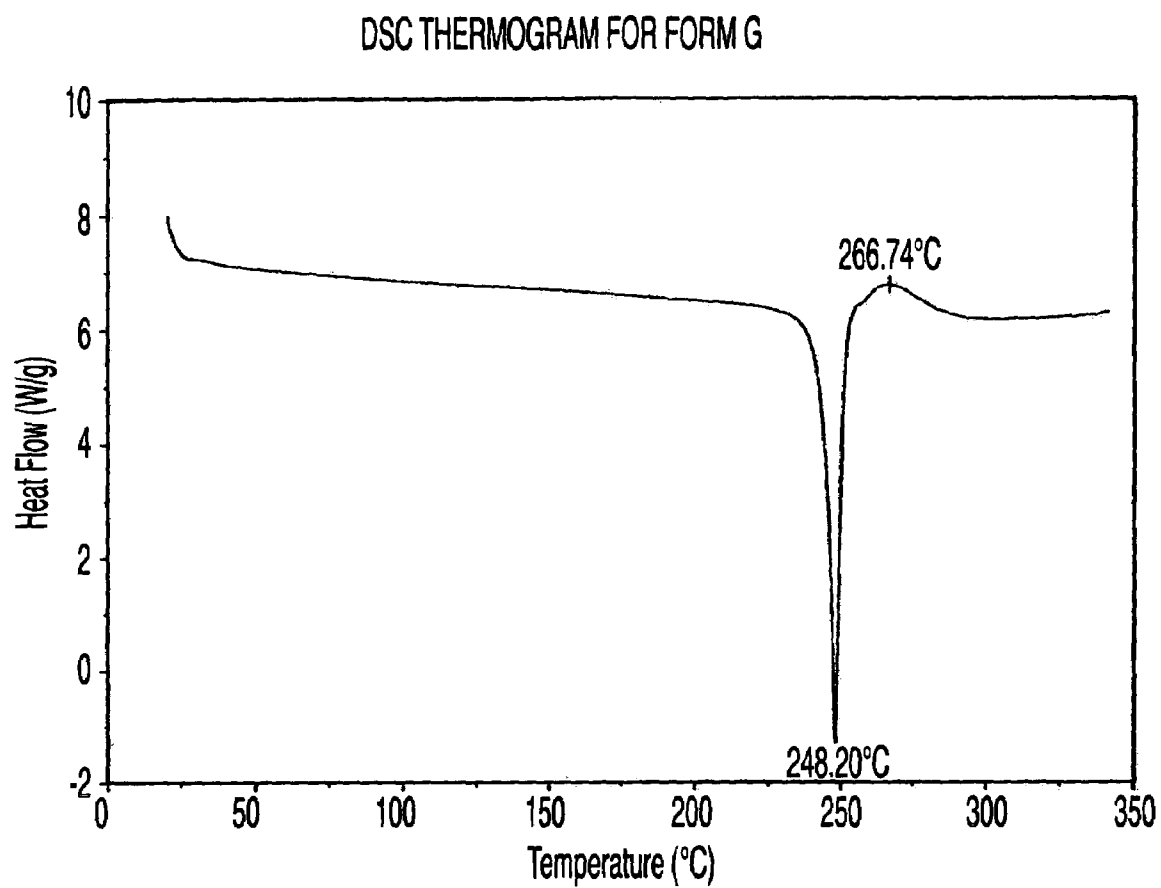


Fig. 29

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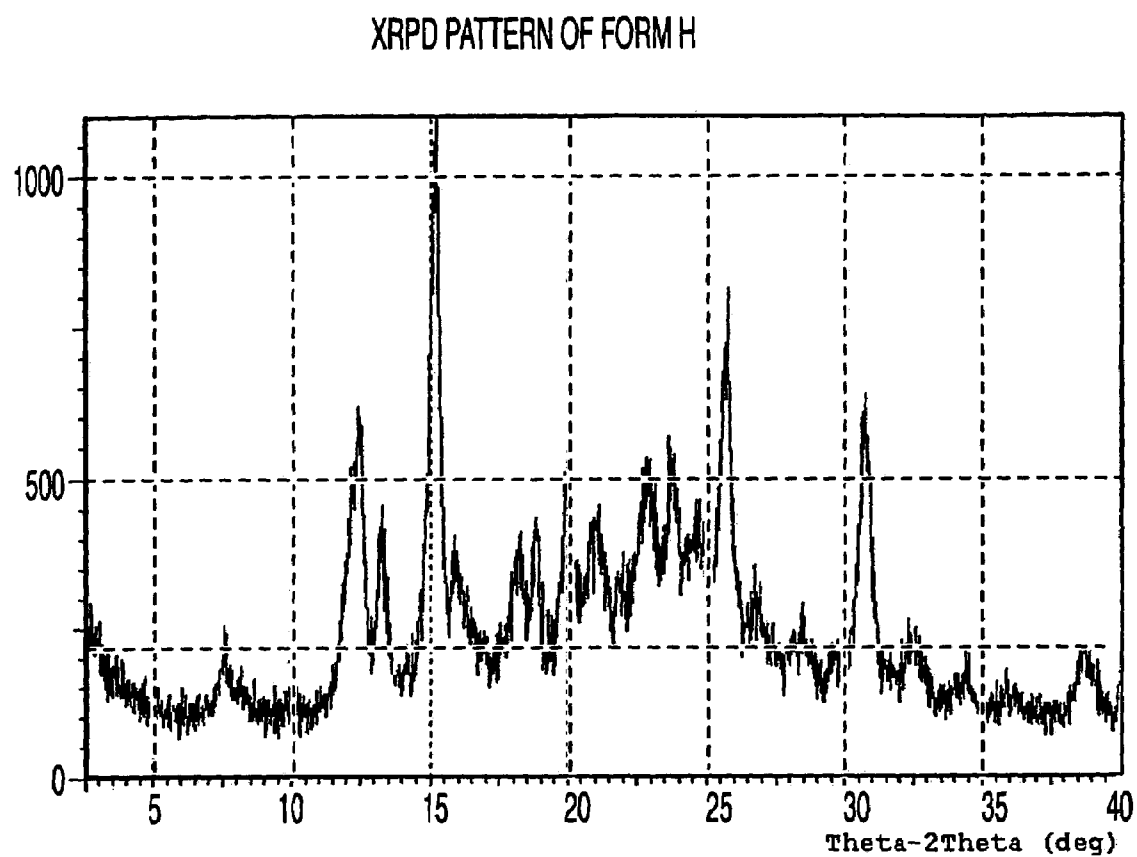


Fig. 30

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TGA (TOP) AND DSC (BOTTOM) OF FORM H

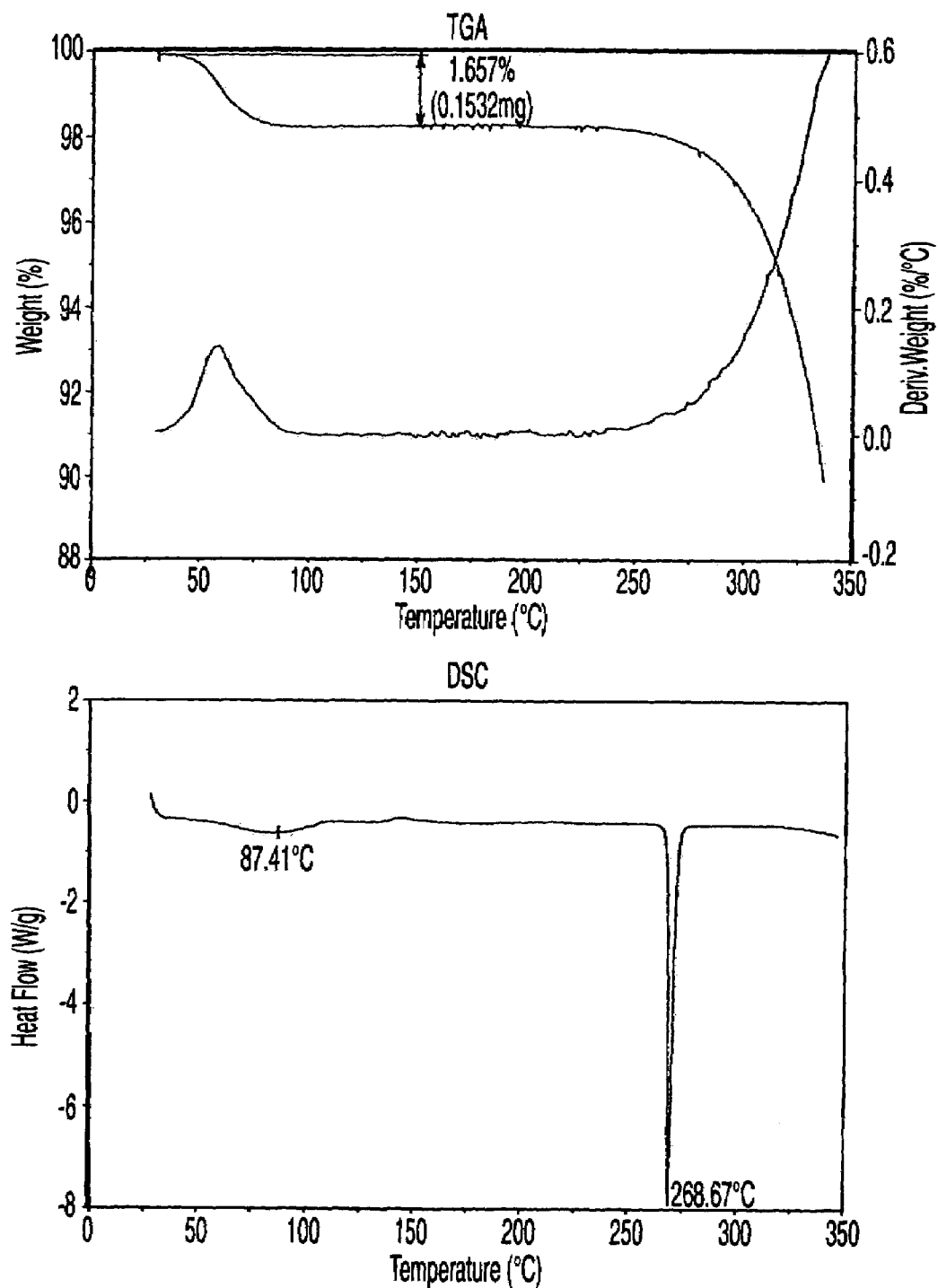


Fig. 31

U.S. Patent

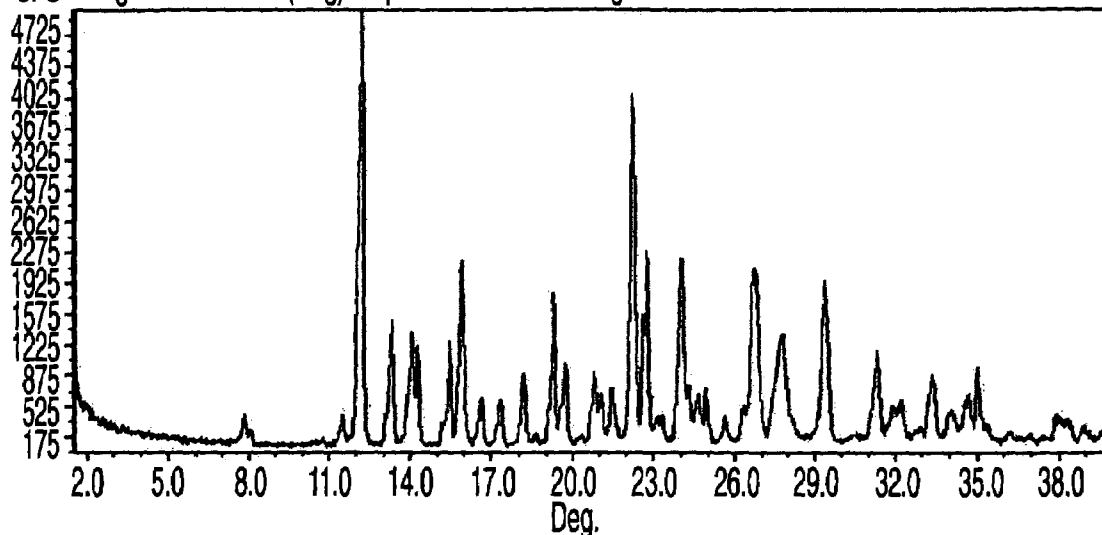
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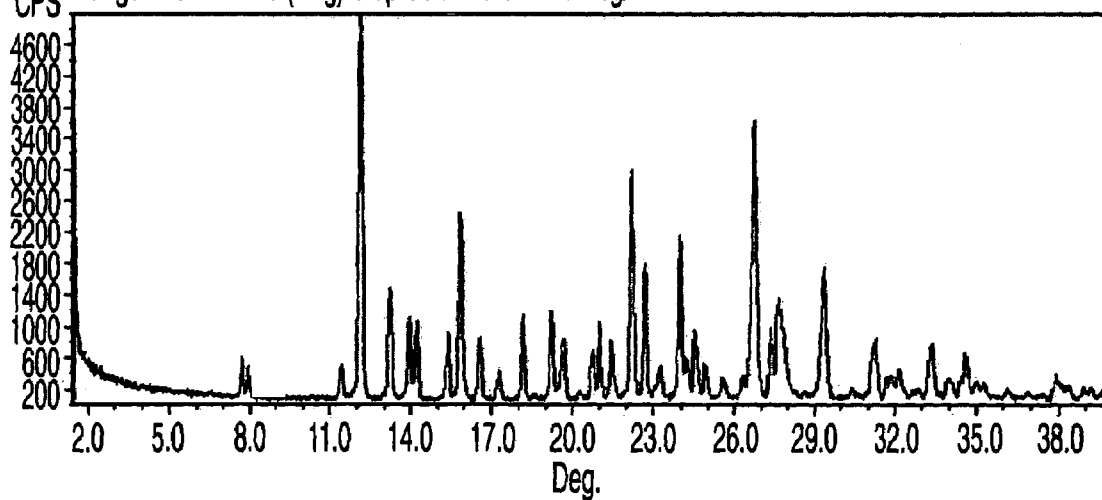
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XRPD PATTERN OF POLYMORPH B

File: Process 5274-104-B
Date: 06-04-04 16:10 Step: 0.020° Cnt Time: 0.500 Sec.
CPS Range: 1.50 - 40.00 (Deg) Step Scan Rate: 2.40 Deg/min

*Fig. 32*

File: Process 5274-100-C XRPD PATTERN OF POLYMORPH B
Date: 06-04-04 16:11 Step: 0.020° Cnt Time: 0.500 Sec.
CPS Range: 1.50 - 40.00 (Deg) Step Scan Rate: 2.40 Deg/min

*Fig. 33*

U.S. Patent

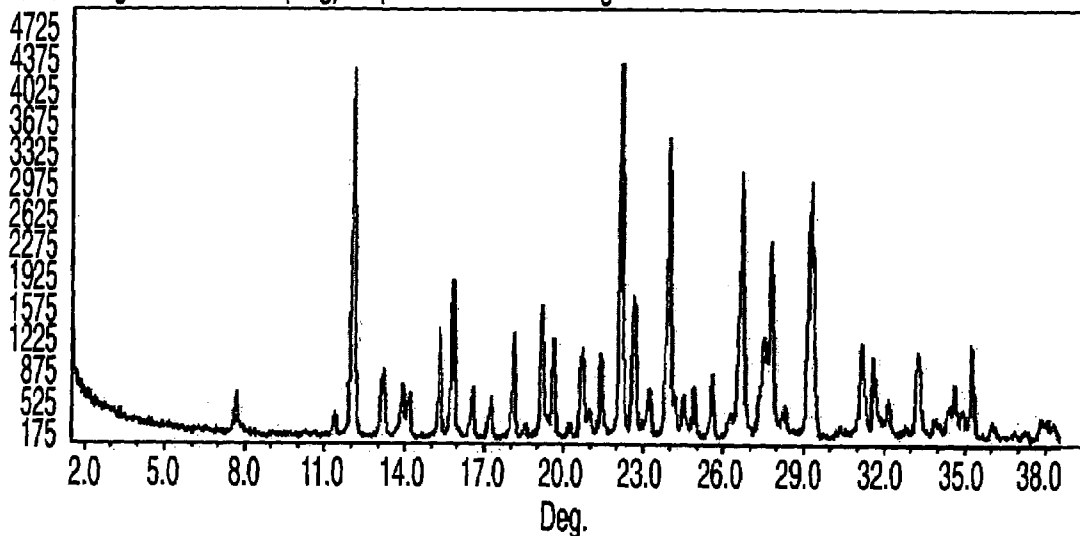
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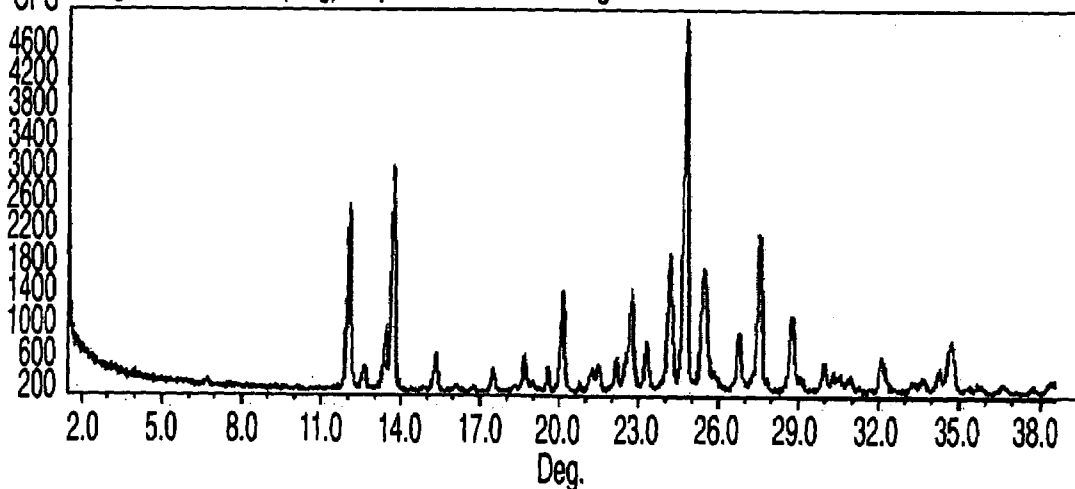
XRPD PATTERN OF POLYMORPH B

File: Process 5274-104-B
Date: 06-04-04 16:10 Step: 0.020° Cnt Time: 0.500 Sec.
CPS Range: 1.50 - 40.00 (Deg) Step Scan Rate: 2.40 Deg/min

*Fig. 34*

XRPD PATTERN OF POLYMORPH E

File: Process 5274-100-C
Date: 06-04-04 16:11 Step: 0.020° Cnt Time: 0.500 Sec.
CPS Range: 1.50 - 40.00 (Deg) Step Scan Rate: 2.40 Deg/min

*Fig. 35*

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XRPD PATTERN OF POLYMORPH MIXTURE

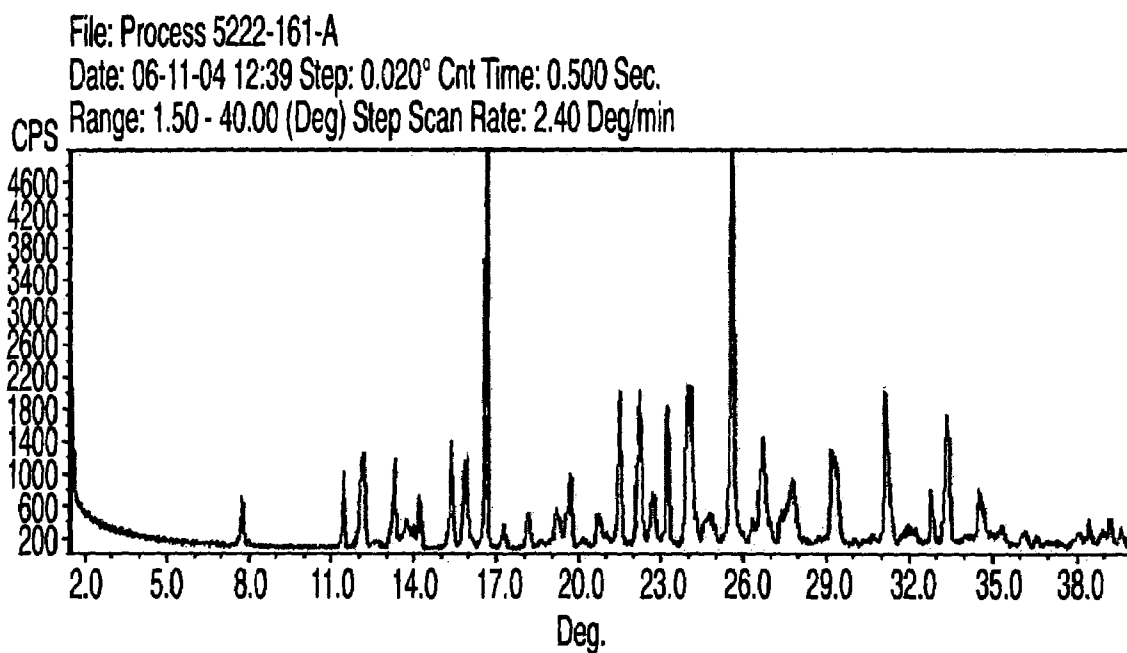


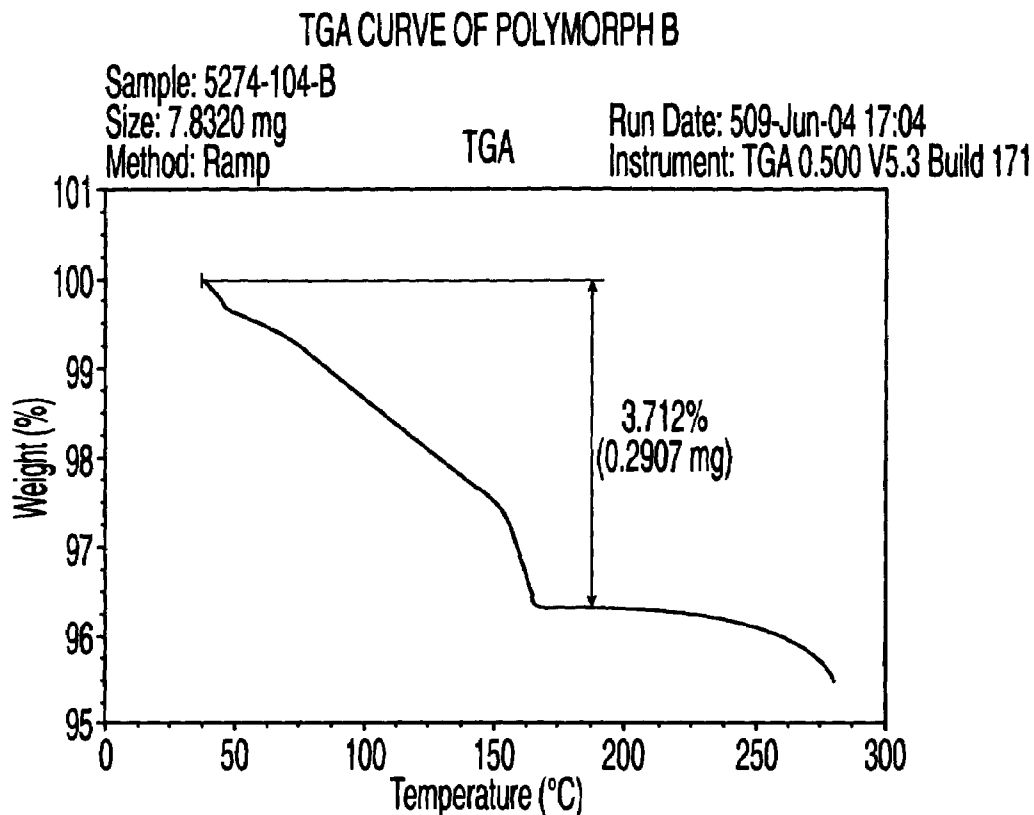
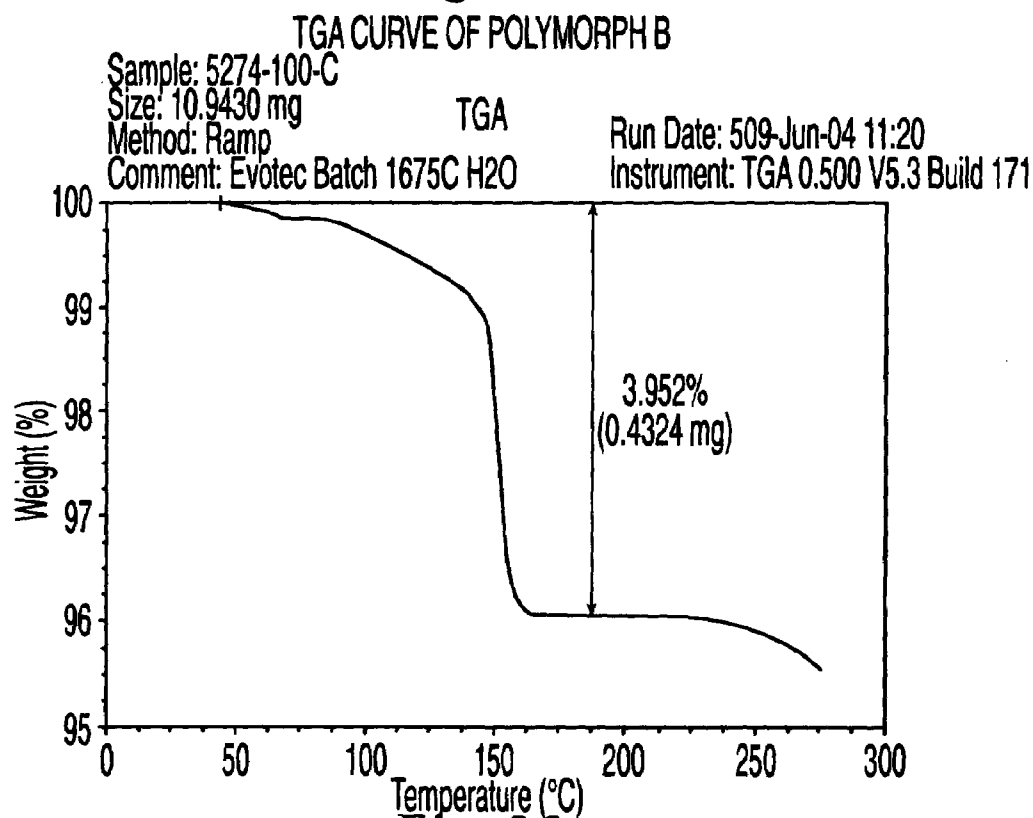
Fig. 36

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*Fig. 37**Fig. 38*

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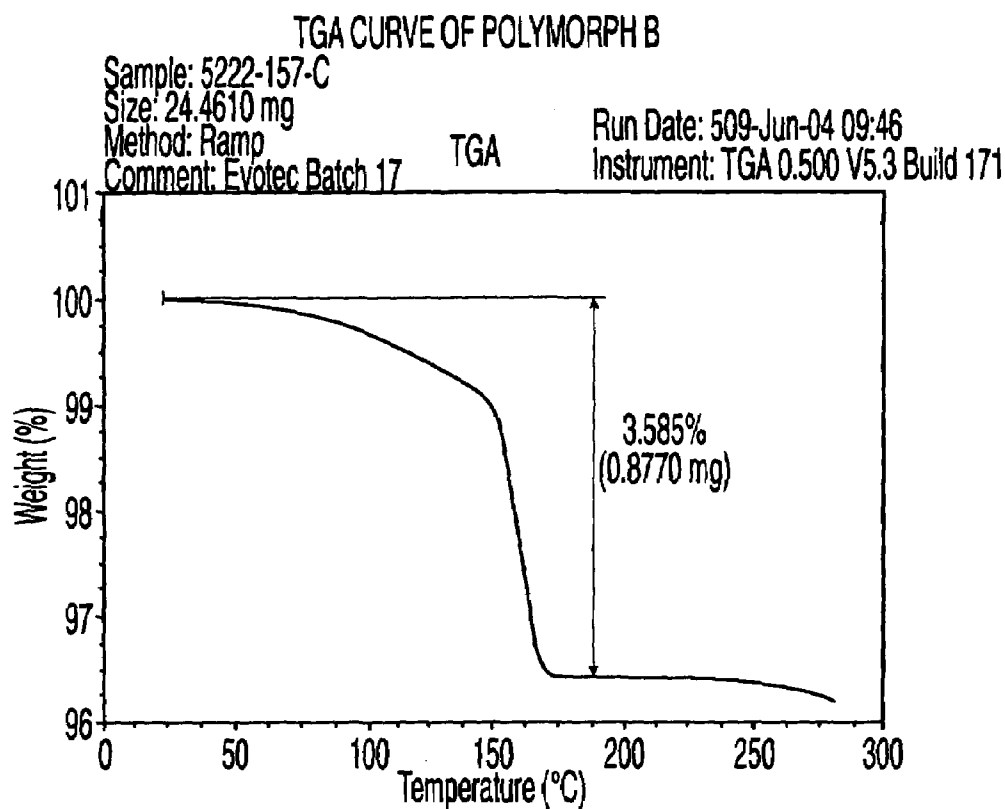


Fig. 39

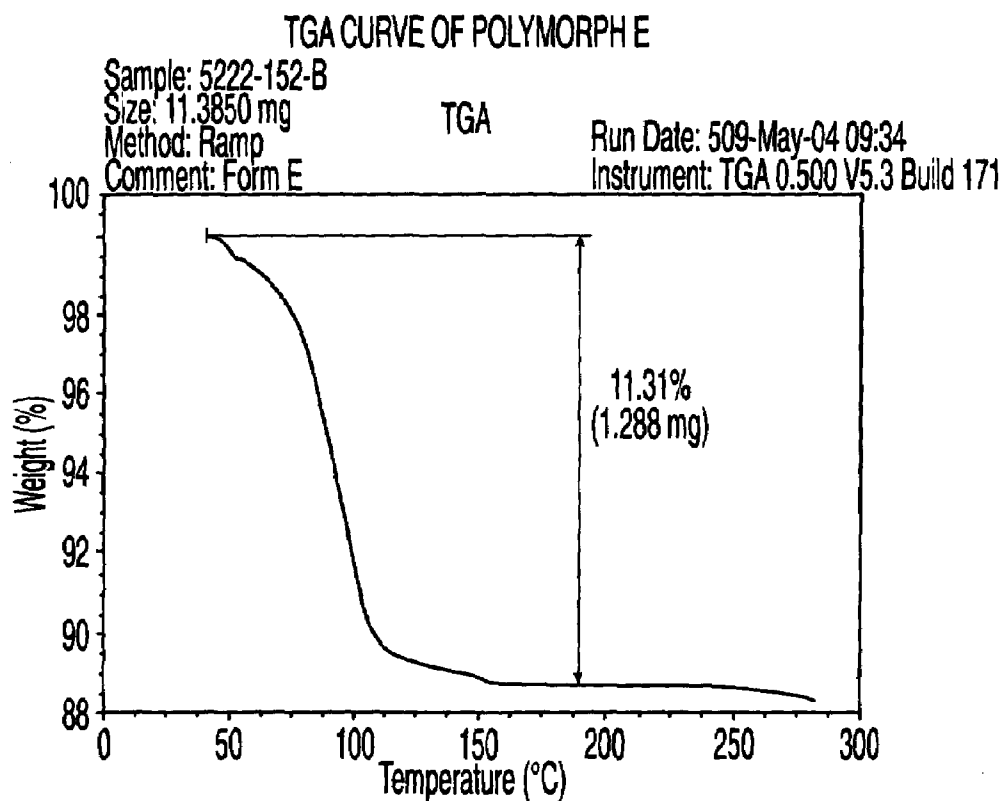


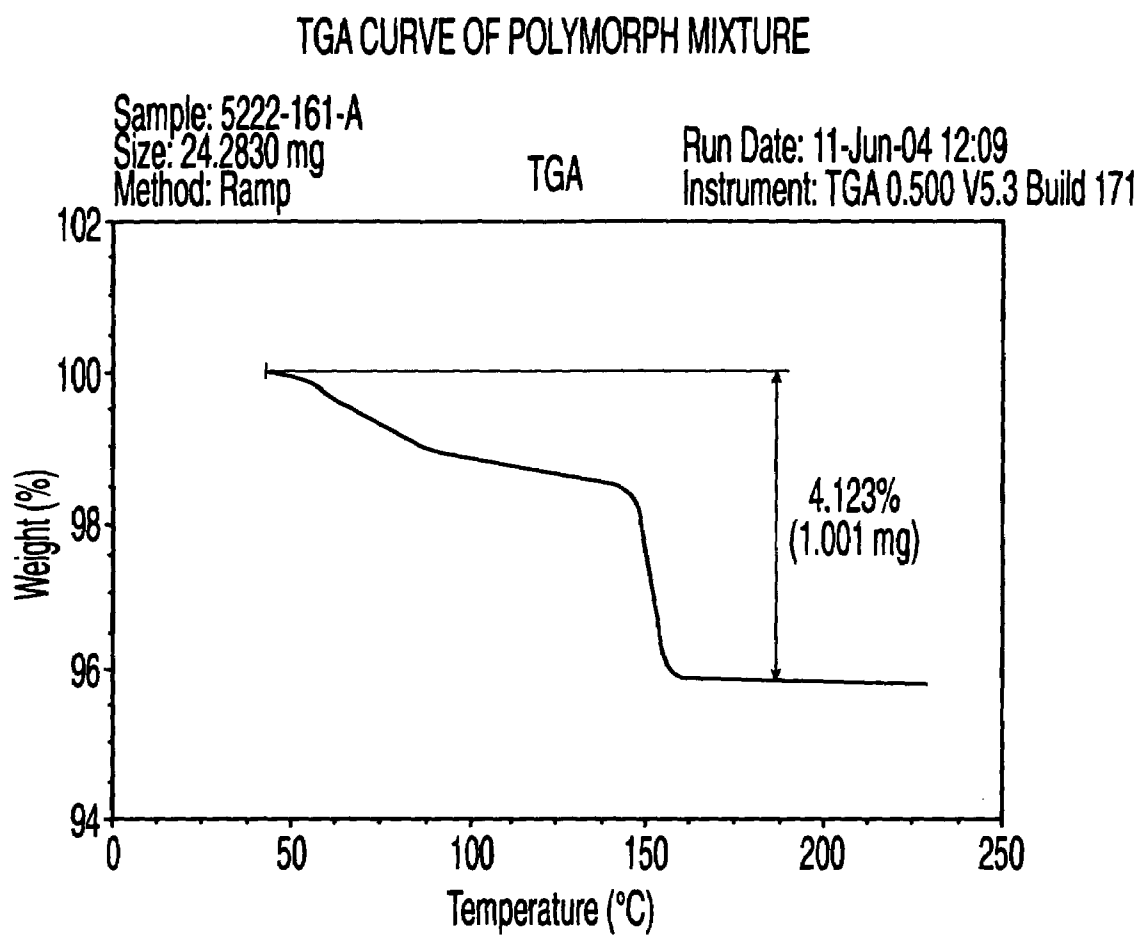
Fig. 40

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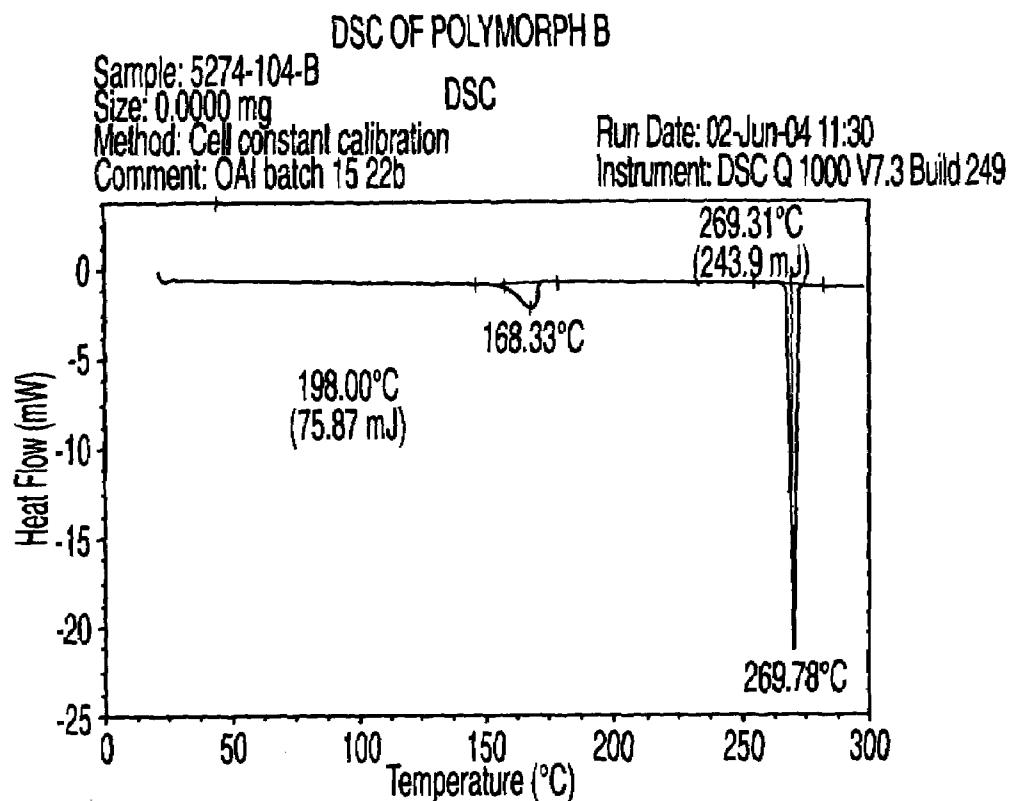
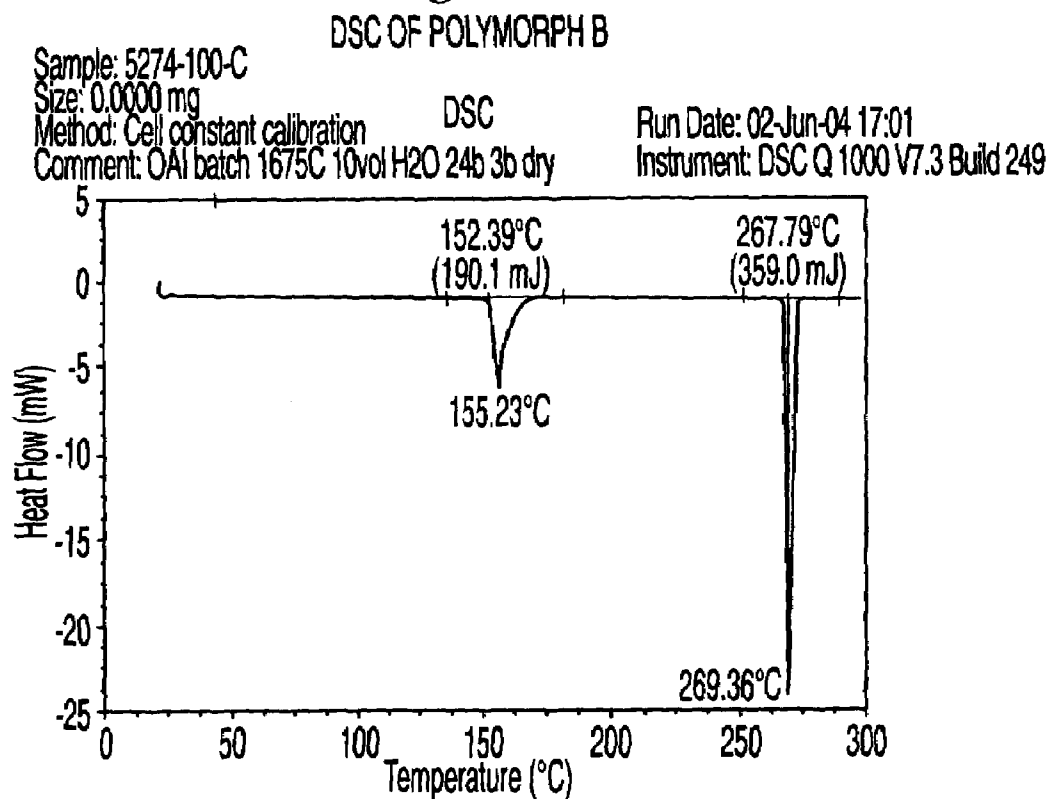
*Fig. 41*

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*Fig. 42**Fig. 43*

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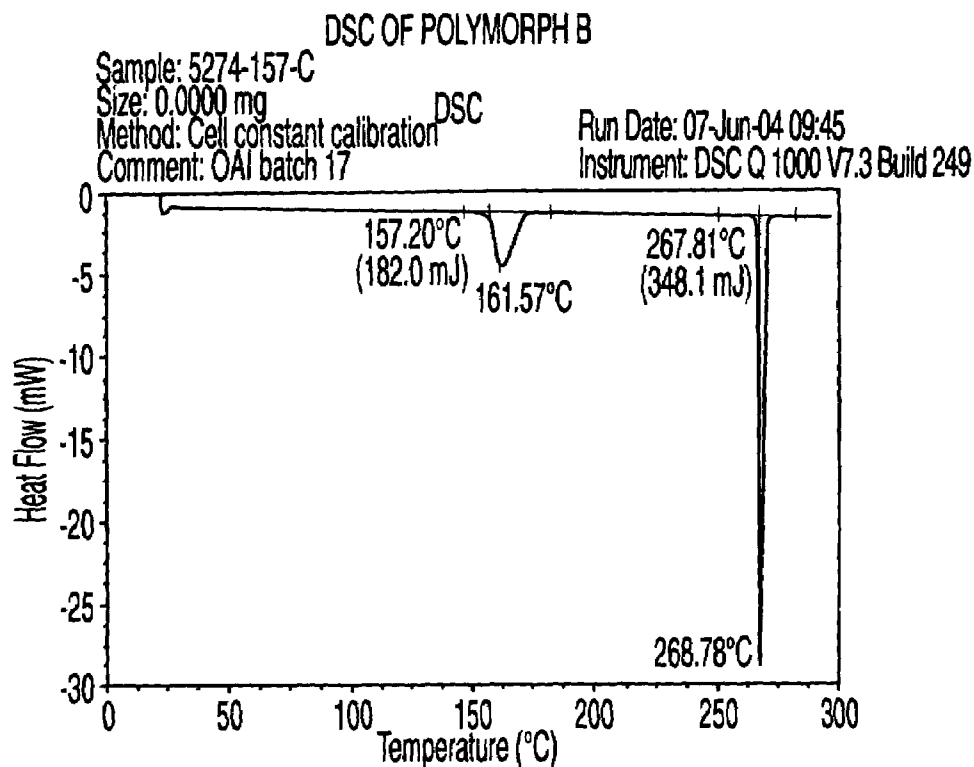


Fig. 44

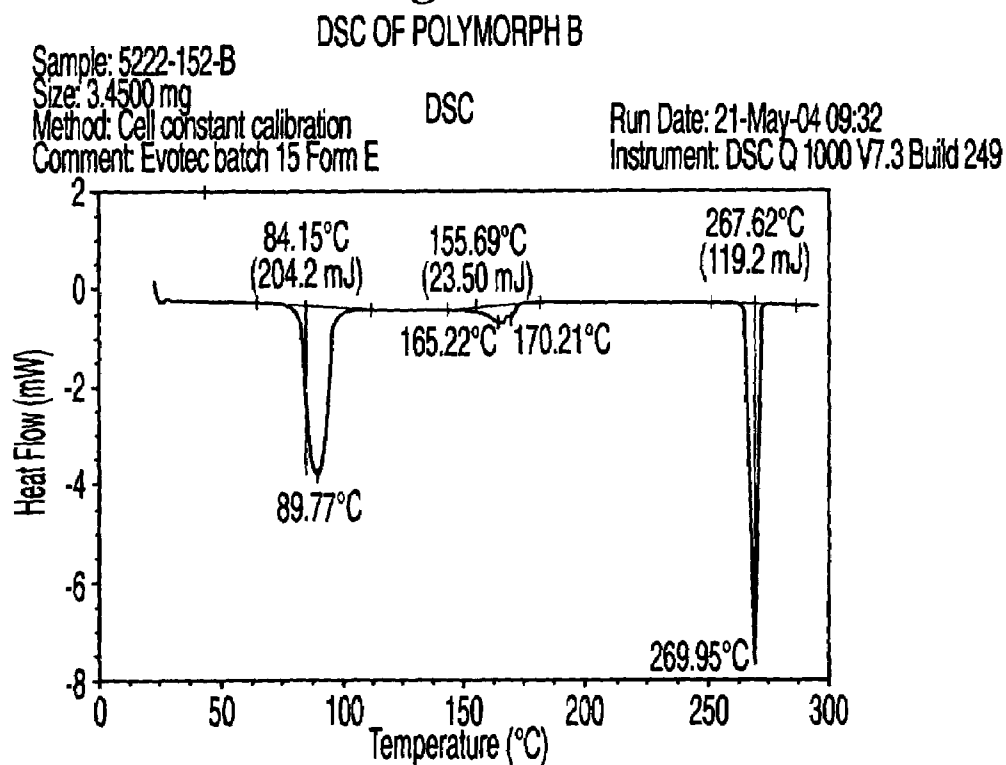


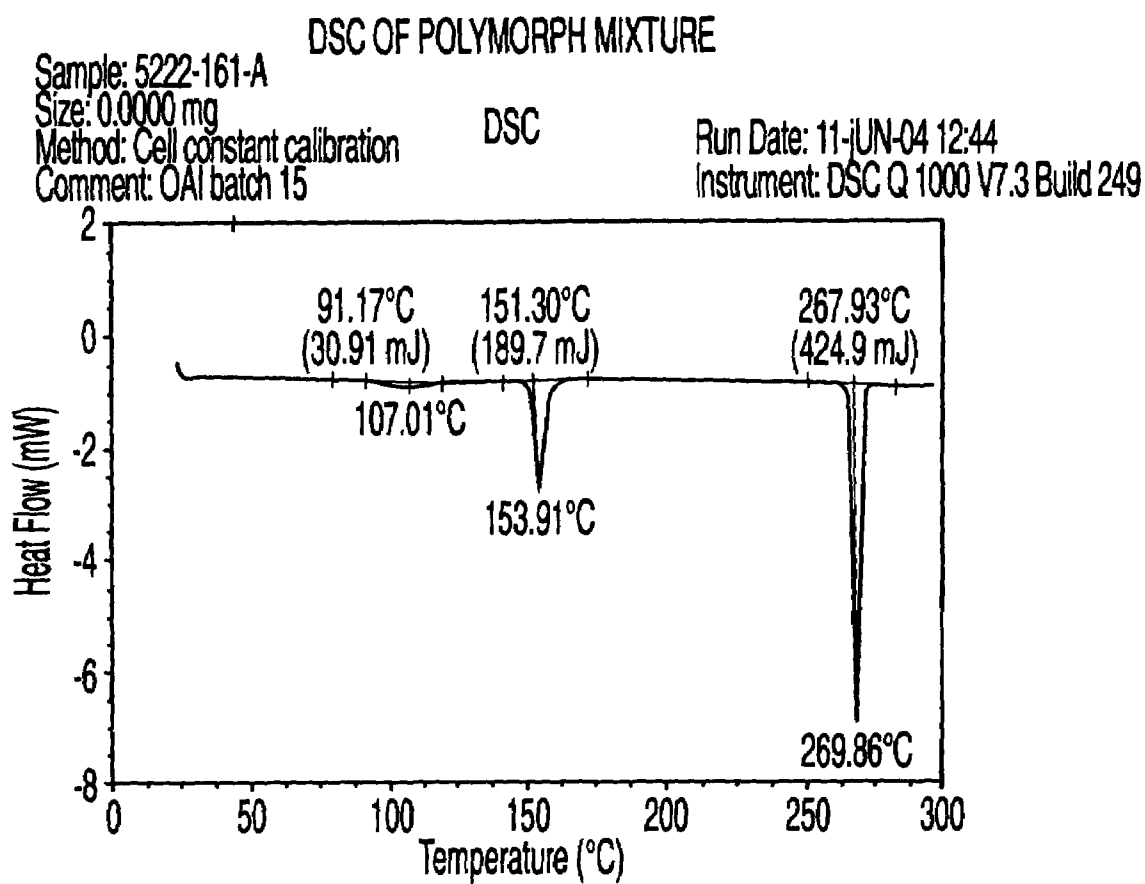
Fig. 45

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*Fig. 46*

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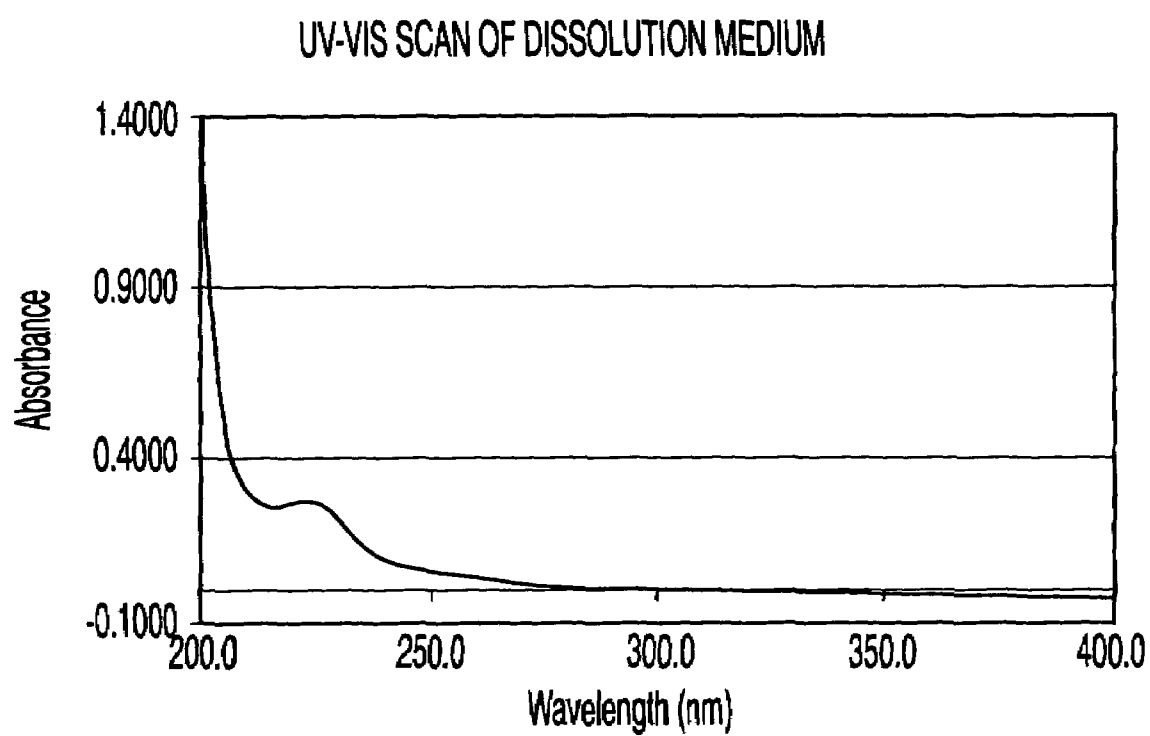


Fig. 47

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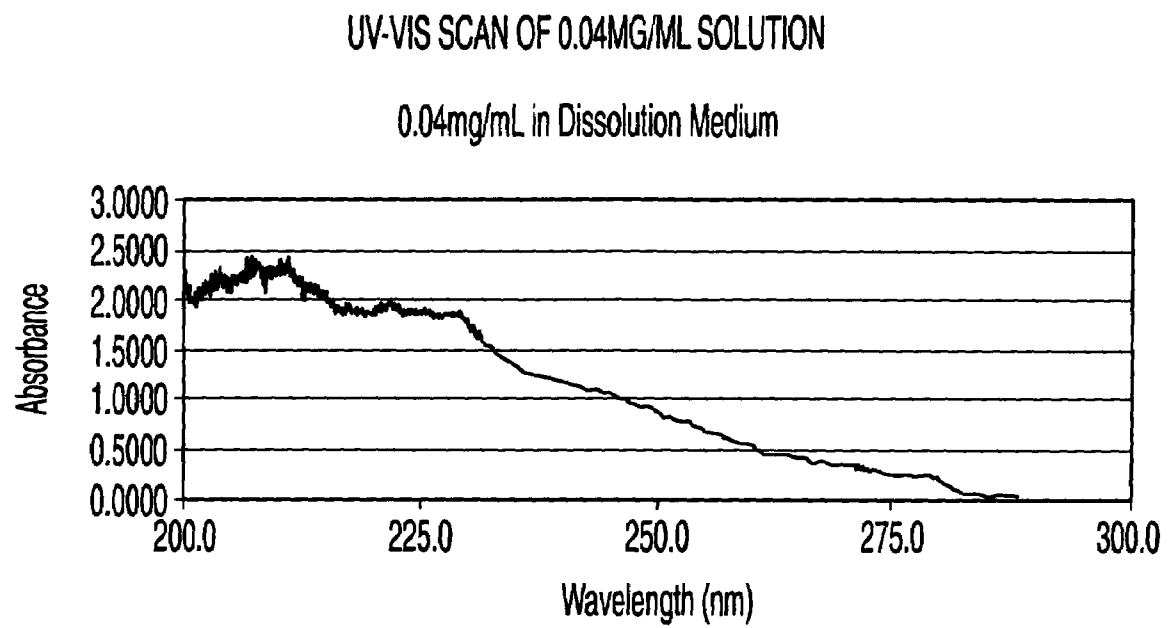


Fig. 48

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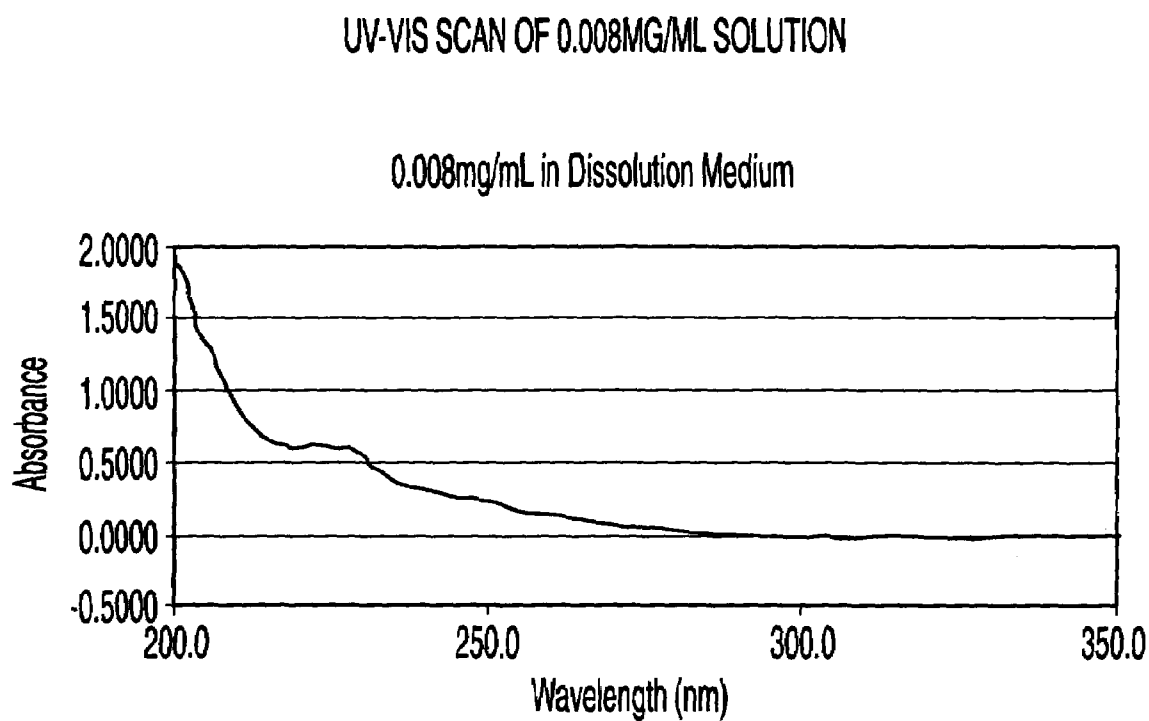
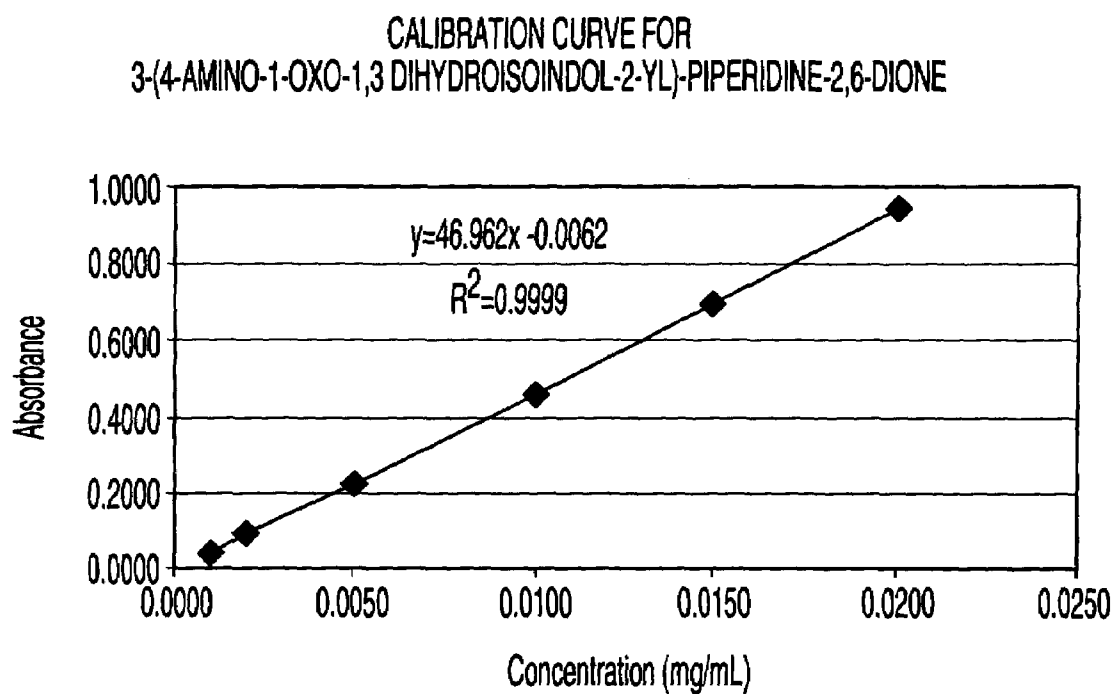


Fig. 49

*Fig. 50*

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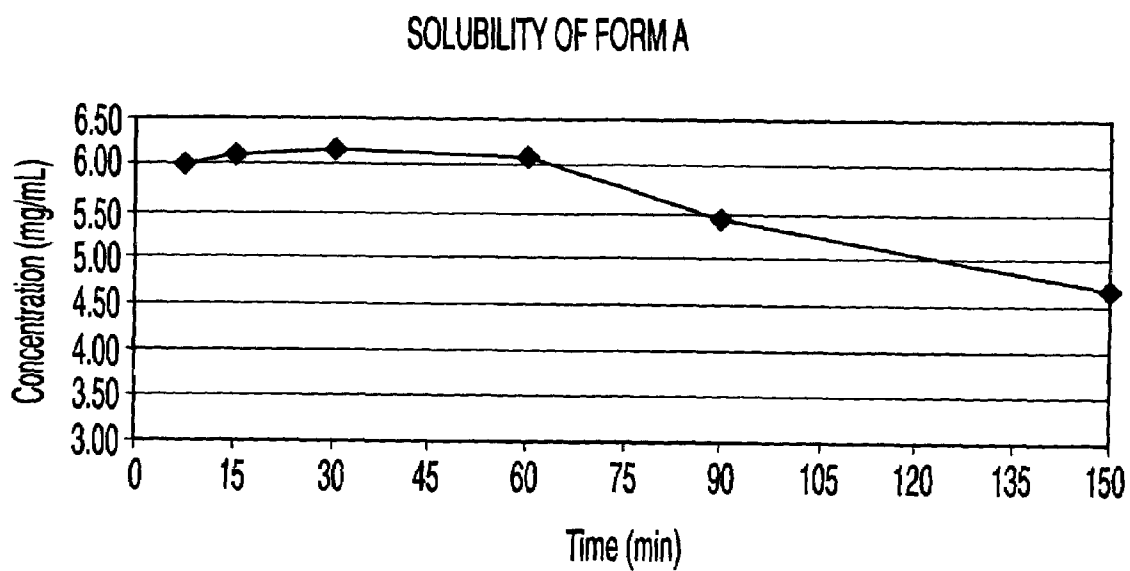


Fig. 51

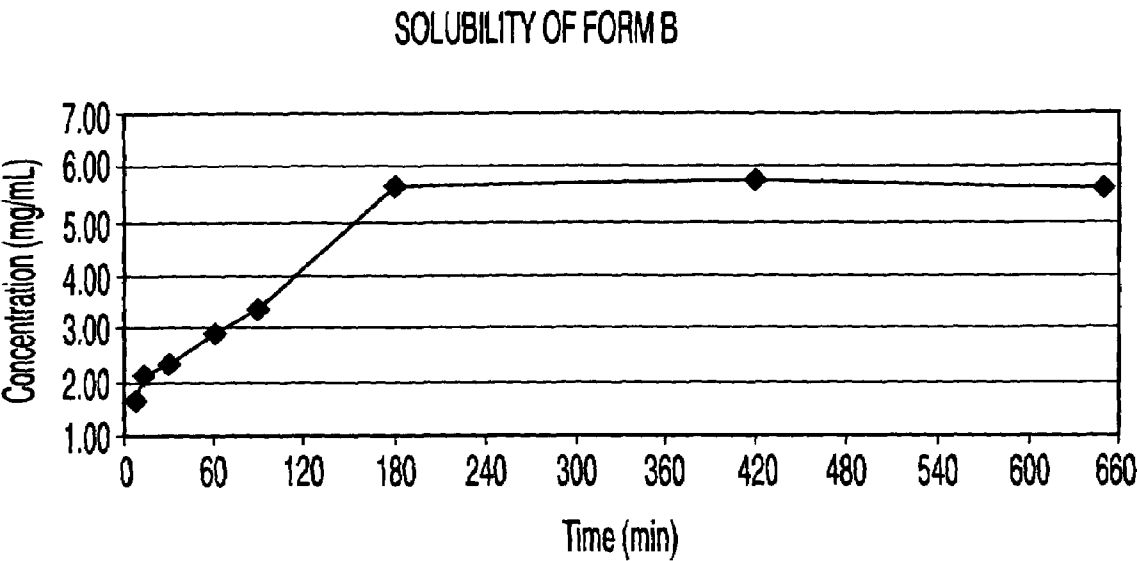


Fig. 52

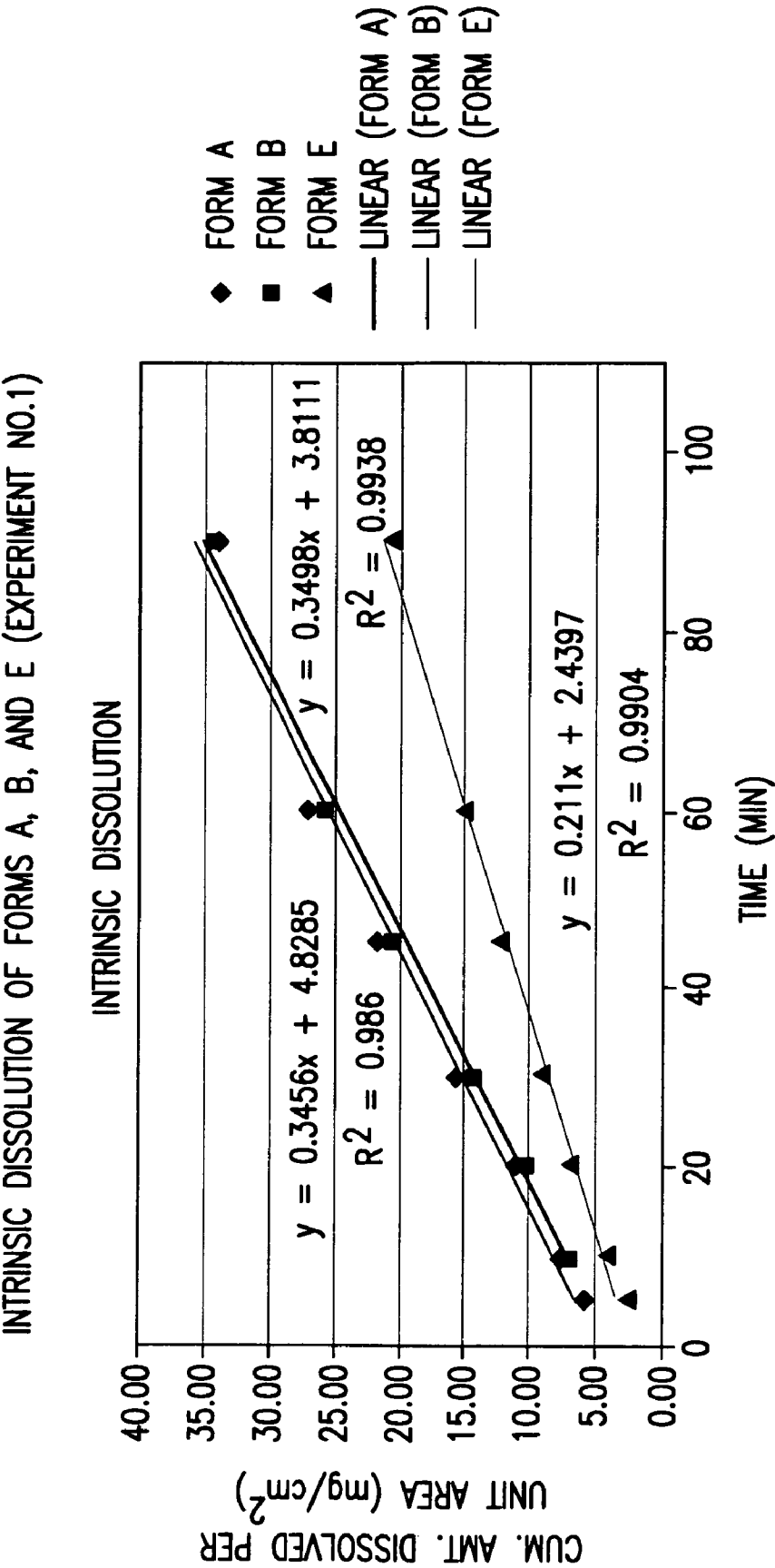


FIG.53

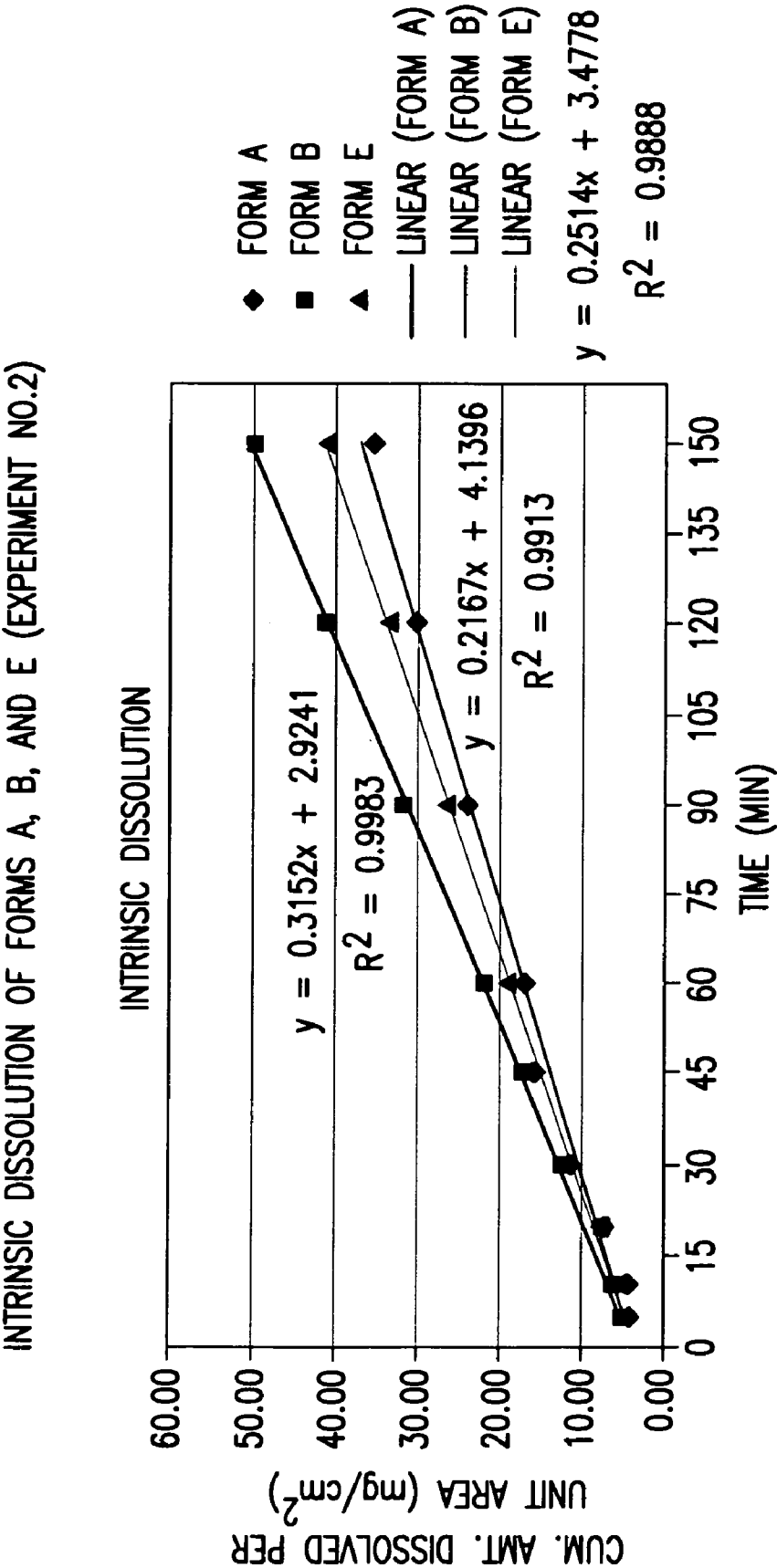


FIG.54

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**POLYMORPHIC FORMS OF
3-(4-AMINO-1-OXO-1,3
DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-
IONE**

This application claims the benefit of U.S. provisional application 60/499,723, filed Sep. 4, 2003, the contents of which are incorporated by reference herein their entirety.

1. FIELD OF THE INVENTION

This invention relates to polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione, compositions comprising the polymorphic forms, methods of making the polymorphic forms and methods of their use for the treatment of diseases and conditions including, but not limited to, inflammatory diseases, autoimmune diseases, and cancer.

2. BACKGROUND OF THE INVENTION

Many compounds can exist in different crystal forms, or polymorphs, which exhibit different physical, chemical, and spectroscopic properties. For example, certain polymorphs of a compound may be more readily soluble in particular solvents, may flow more readily, or may compress more easily than others. See, e.g., P. DiMartino, et al., *J. Thermal Anal.*, 48:447-458 (1997). In the case of drugs, certain solid forms may be more bioavailable than others, while others may be more stable under certain manufacturing, storage, and biological conditions. This is particularly important from a regulatory standpoint, since drugs are approved by agencies such as the U.S. Food and Drug Administration only if they meet exacting purity and characterization standards. Indeed, the regulatory approval of one polymorph of a compound, which exhibits certain solubility and physico-chemical (including spectroscopic) properties, typically does not imply the ready approval of other polymorphs of that same compound.

Polymorphic forms of a compound are known in the pharmaceutical arts to affect, for example, the solubility, stability, flowability, fractability, and compressibility of the compound, as well as the safety and efficacy of drug products comprising it. See, e.g., Knapman, K. *Modern Drug Discoveries*, 2000, 53. Therefore, the discovery of new polymorphs of a drug can provide a variety of advantages.

U.S. Pat. Nos. 5,635,517 and 6,281,230, both to Muller et al., disclose 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione, which is useful in treating and preventing a wide range of diseases and conditions including, but not limited to, inflammatory diseases, autoimmune diseases, and cancer. New polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione can further the development of formulations for the treatment of these chronic illnesses, and may yield numerous formulation, manufacturing and therapeutic benefits.

3. SUMMARY OF THE INVENTION

This invention encompasses polymorphs of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. In certain aspects, the invention provides polymorphs of the compound identified herein as forms A, B, C, D, E, F, G, and H. The invention also encompasses mixtures of these forms. In further embodiments, this invention provides methods of making, isolating and characterizing the polymorphs.

This invention also provides pharmaceutical compositions and single unit dosage forms comprising a polymorph of

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3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. The invention further provides methods for the treatment or prevention of a variety of diseases and disorders, which comprise administering to a patient in need of such treatment or prevention a therapeutically effective amount of a polymorph of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione.

4. BRIEF DESCRIPTION OF THE DRAWINGS

Specific aspects of the invention can be understood with reference to the attached figures:

FIG. 1 provides a representative X-ray powder diffraction (XRPD) pattern of Form A;

FIG. 2 provides a representative IR spectrum of Form A;

FIG. 3 provides a representative Raman spectrum of Form A;

FIG. 4 provides a representative thermogravimetric analysis (TGA) curve and a representative differential scanning calorimeter (DSC) thermogram of Form A;

FIG. 5 provides a representative moisture sorption/desorption isotherm of Form A;

FIG. 6 provides a representative XRPD pattern of Form B;

FIG. 7 provides a representative IR spectrum of Form B;

FIG. 8 provides a representative Raman spectrum of Form B;

FIG. 9 provides a representative TGA curve and a representative DSC thermogram of Form B;

FIG. 10 provides representative TG-IR results of Form B;

FIG. 11 provides a representative moisture sorption/desorption isotherm of Form B;

FIG. 12 provides a representative XRPD pattern of Form C;

FIG. 13 provides a representative IR spectrum of Form C;

FIG. 14 provides a representative Raman spectrum of Form C;

FIG. 15 provides a representative TGA curve and a representative DSC thermogram of Form C;

FIG. 16 provides representative TG-IR results of Form C;

FIG. 17 provides a representative moisture sorption/desorption isotherm of Form C;

FIG. 18 provides a representative XRPD pattern of Form D;

FIG. 19 provides a representative IR spectrum of Form D;

FIG. 20 provides a representative Raman spectrum of Form D;

FIG. 21 provides a representative TGA curve and a representative DSC thermogram of Form D;

FIG. 22 provides a representative moisture sorption/desorption isotherm of Form D;

FIG. 23 provides a representative XRPD pattern of Form E;

FIG. 24 provides a representative TGA curve and a representative DSC thermogram of Form E;

FIG. 25 provides a representative moisture sorption/desorption isotherm of Form E;

FIG. 26 provides a representative XRPD pattern for a sample of Form F;

FIG. 27 provides a representative thermogram of Form F;

FIG. 28 provides a representative XRPD pattern of Form G;

FIG. 29 provides a representative DSC thermogram for a sample of Form G;

FIG. 30 provides a representative XRPD pattern of Form H;

FIG. 31 provides a representative TGA curve and a representative DSC thermogram of Form H;

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FIG. 32 provides a representative XRPD pattern of Form B;

FIG. 33 provides a representative XRPD pattern of Form B;

FIG. 34 provides a representative XRPD pattern of Form B;

FIG. 35 provides a representative XRPD pattern of Form E;

FIG. 36 provides a representative XRPD pattern of polymorph mixture;

FIG. 37 provides a representative TGA curve of Form B;

FIG. 38 provides a representative TGA curve of Form B;

FIG. 39 provides a representative TGA curve of Form B;

FIG. 40 provides a representative TGA curve of Form E;

FIG. 41 provides a representative TGA curve of polymorph mixture;

FIG. 42 provides a representative DSC thermogram of Form B;

FIG. 43 provides a representative DSC thermogram of Form B;

FIG. 44 provides a representative DSC thermogram of Form B;

FIG. 45 provides a representative DSC thermogram of Form E;

FIG. 46 provides a representative DSC thermogram of polymorph mixture;

FIG. 47 provides a UV-Vis scan of dissolution medium;

FIG. 48 provides a UV-Vis scan of 0.04 mg/ml of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione in dissolution medium;

FIG. 49 provides a UV-Vis scan of 0.008 mg/ml of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione in dissolution medium;

FIG. 50 provides a calibration curve for 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione;

FIG. 51 provides a solubility curve of Form A;

FIG. 52 provides a solubility curve of Form B;

FIG. 53 provides an intrinsic dissolution of Forms A, B and E; and

FIG. 54 provides an intrinsic dissolution of Forms A, B and E.

5. DETAILED DESCRIPTION OF THE INVENTION

5.1 Definitions

As used herein and unless otherwise indicated, the terms “treat,” “treating” and “treatment” refer to the alleviation of a disease or disorder and/or at least one of its attendant symptoms.

As used herein and unless otherwise indicated, the terms “prevent,” “preventing” and “prevention” refer to the inhibition of a symptom of a disease or disorder or the disease itself.

As used herein and unless otherwise indicated, the terms “polymorph” and “polymorphic form” refer to solid crystalline forms of a compound or complex. Different polymorphs of the same compound can exhibit different physical, chemical and/or spectroscopic properties. Different physical properties include, but are not limited to stability (e.g., to heat or light), compressibility and density (important in formulation and product manufacturing), and dissolution rates (which can affect bioavailability). Differences in stability can result from changes in chemical reactivity (e.g., differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical characteristics (e.g., tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both

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(e.g., tablets of one polymorph are more susceptible to breakdown at high humidity). Different physical properties of polymorphs can affect their processing. For example, one polymorph might be more likely to form solvates or might be more difficult to filter or wash free of impurities than another due to, for example, the shape or size distribution of particles of it.

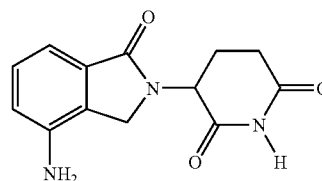
Polymorphs of a molecule can be obtained by a number of methods known in the art. Such methods include, but are not limited to, melt recrystallization, melt cooling, solvent recrystallization, desolvation, rapid evaporation, rapid cooling, slow cooling, vapor diffusion and sublimation. Polymorphs can be detected, identified, classified and characterized using well-known techniques such as, but not limited to, differential scanning calorimetry (DSC), thermogravimetry (TGA), X-ray powder diffractometry (XRPD), single crystal X-ray diffractometry, vibrational spectroscopy, solution calorimetry, solid state nuclear magnetic resonance (NMR), infrared (IR) spectroscopy, Raman spectroscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility, and rate of dissolution.

As used herein to refer to the spectra or data presented in graphical form (e.g., XRPD, IR, Raman and NMR spectra), and unless otherwise indicated, the term “peak” refers to a peak or other special feature that one skilled in the art would recognize as not attributable to background noise. The term “significant peaks” refers to peaks at least the median size (e.g., height) of other peaks in the spectrum or data, or at least 1.5, 2, or 2.5 times the median size of other peaks in the spectrum or data.

As used herein and unless otherwise indicated, the term “substantially pure” when used to describe a polymorph of a compound means a solid form of the compound that comprises that polymorph and is substantially free of other polymorphs of the compound. A representative substantially pure polymorph comprises greater than about 80% by weight of one polymorphic form of the compound and less than about 20% by weight of other polymorphic forms of the compound, more preferably greater than about 90% by weight of one polymorphic form of the compound and less than about 10% by weight of the other polymorphic forms of the compound, even more preferably greater than about 95% by weight of one polymorphic form of the compound and less than about 5% by weight of the other polymorphic forms of the compound, and most preferably greater than about 97% by weight of one polymorphic forms of the compound and less than about 3% by weight of the other polymorphic forms of the compound.

5.2 Polymorphic Forms

This invention is directed to polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione, which has the structure shown below:



This compound can be prepared according to the methods described in U.S. Pat. Nos. 6,281,230 and 5,635,517, the

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entireties of which are incorporated herein by reference. For example, the compound can be prepared through catalytic hydrogenation of 3-(4-nitro-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. 3-(4-Nitro-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione can be obtained by allowing 2,6-dioxopiperidin-3-ammonium chloride to react with methyl 2-bromomethyl-4-nitrobenzoate in dimethylformamide in the presence of triethylamine. The methyl 2-bromomethyl-4-nitrobenzoate in turn is obtained from the corresponding methyl ester of nitro-ortho-toluic acid by conventional bromination with N-bromosuccinimide under the influence of light.

Polymorphs of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione can be obtained by techniques known in the art, including solvent recrystallization, desolvation, vapor diffusion, rapid evaporation, slow evaporation, rapid cooling and slow cooling. Polymorphs can be made by dissolving a weighed quantity of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione in various solvents at elevated temperatures. The solutions of the compound can then be filtered and allowed to evaporate either in an open vial (for fast hot evaporation) or in a vial covered with aluminum foil containing pinholes (hot slow evaporation). Polymorphs can also be obtained from slurries. Polymorphs can be crystallized from solutions or slurries using several methods. For example, a solution created at an elevated temperature (e.g., 60° C.) can be filtered quickly then allowed to cool to room temperature. Once at room temperature, the sample that did not crystallize can be moved to a refrigerator then filtered. Alternatively, the solutions can be crash cooled by dissolving the solid in a solvent at an increased temperature (e.g., 45-65° C.) followed by cooling in a dry ice/solvent bath.

One embodiment of the invention encompasses Form A of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form A is an unsolvated, crystalline material that can be obtained from non-aqueous solvent systems. Another embodiment of the invention encompasses Form B of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form B is a hemihydrated, crystalline material that can be obtained from various solvent systems. Another embodiment of the invention encompasses Form C of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form C is a hemisolvated crystalline material that can be obtained from solvents such as, but not limited to, acetone. Another embodiment of the invention encompasses Form D of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form D is a crystalline, solvated polymorph prepared from a mixture of acetonitrile and water. Another embodiment of the invention encompasses Form E of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form E is a dihydrated, crystalline material. Another embodiment of the invention encompasses Form F of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form F is an unsolvated, crystalline material that can be obtained from the dehydration of Form E. Another embodiment of the invention encompasses Form G of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form G is an unsolvated, crystalline material that can be obtained from slurrying forms B and E in a solvent such as, but not limited to, tetrahydrofuran (THF). Another embodiment of the invention encompasses Form H of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form H is a partially hydrated crystalline material that can be obtained by exposing Form E to 0% relative humidity. Each of these forms is discussed in detail below.

Another embodiment of the invention encompasses a composition comprising amorphous 3-(4-amino-1-oxo-1,3 dihy-

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dro-isoindol-2-yl)-piperidine-2,6-dione and crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione of form A, B, C, D, E, F, G or H. Specific compositions can comprise greater than about 50, 75, 90 or 95 weight percent crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione.

Another embodiment of the invention encompasses a composition comprising at least two crystalline forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione (e.g., a mixture of polymorph forms B and E).

5.2.1 Form A

The data described herein for Form A, as well as for Forms B-H, were obtained using the experimental methods described in Examples 6.3-6.7, provided below.

Form A can be obtained from various solvents, including, but not limited to 1-butanol, butyl acetate, ethanol, ethyl acetate, methanol, methyl ethyl ketone, and THF. FIG. 1 shows a representative XRPD pattern of Form A. The pattern is characterized by peaks, preferably significant peaks, at approximately 8, 14.5, 16, 17.5, 20.5, 24, and 26 degrees 2 θ . Representative IR and Raman spectra data are provided in FIGS. 2 and 3.

Representative thermal characteristics of Form A are shown in FIG. 4. TGA data show a small weight increase up to about 150° C., indicating an unsolvated material. Weight loss above 150° C. is attributed to decomposition. The DSC curve of Form A exhibits an endotherm at about 270° C.

Representative moisture sorption and desorption data are plotted in FIG. 5. Form A does not exhibit a significant weight gain from 5 to 95% relative humidity. Equilibrium can be obtained at each relative humidity step. As the form dries from 95% back down to 5% relative humidity, it tends to maintain its weight such that at 5% relative humidity it has typically lost only about 0.003% by weight from start to finish. Form A is capable of remaining a crystalline solid for about 11 days when stored at about 22, 45, 58, and 84% relative humidity.

Interconversion studies show that Form A can convert to Form B in aqueous solvent systems and can convert to Form C in acetone solvent systems. Form A tends to be stable in anhydrous solvent systems. In water systems and in the presence of Form E, Form A tends to convert to Form E.

When stored for a period of about 85 days under two different temperature/relative humidity stress conditions (room temperature/0% relative humidity (RH) and 40° C./93% RH), Form A typically does not convert to a different form.

In sum, Form A is a crystalline, unsolvated solid that melts at approximately 270° C. Form A is weakly or not hygroscopic and appears to be the most thermodynamically stable anhydrous polymorph of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione discovered thus far.

5.2.2 Form B

Form B can be obtained from many solvents, including, but not limited to, hexane, toluene, and water. FIG. 6 shows a representative XRPD pattern of Form B, characterized by peaks at approximately 16, 18, 22 and 27 degrees 2 θ .

Solution proton NMR confirm that Form B is a form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Representative IR and Raman spectra are shown in FIGS. 7 and 8, respectively. Compared to Form A, the IR spectrum for Form B has peaks at approximately 3513 and 1960 cm⁻¹.

Representative DSC and TGA data for Form B are shown in FIG. 9. The DSC curve exhibits endotherms at about 146 and 268° C. These events are identified as dehydration and melting by hot stage microscopy experiments. Form B typi-

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cally loses about 3.1% volatiles up to about 175° C. (per approximately 0.46 moles of water). Comparison of the IR spectrum of the volatiles with that of water indicates that they are water (See FIG. 10). Calculations from TGA data indicate that Form B is a hemihydrate. Karl Fischer water analysis also

Representative moisture sorption and desorption data are shown in FIG. 11. Form B typically does not exhibit a significant weight gain from 5% to 95% relative humidity, when equilibrium is obtained at each relative humidity step. As Form B dries from 95% back down to 5% relative humidity, it tends to maintain its weight such that at 5% relative humidity it typically has gained only about 0.022% by weight (about 0.003 mg) from start to finish. Form B does not convert to a different form upon exposure to about 84% relative humidity for about ten days.

Interconversion studies show that Form B typically converts to Form A in a THF solvent system, and typically converts to Form C in an acetone solvent system. In aqueous solvent systems such as pure water and 10% water solutions, Form B is the most stable of the polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. However, it can convert to Form E in the presence of water. Desolvation experiments show that upon heating at about 175° C. for about five minutes, Form B typically converts to Form A.

When stored for a period of about 85 days under two different temperature/relative humidity stress conditions (room temperature/0% RH and 40° C./93% RH), Form B does not convert to a different form.

In sum, Form B is a hemihydrated, crystalline solid which has a DSC thermogram exhibiting endotherms at about 146 and about 268° C. Interconversion studies show that Form B converts to Form E in aqueous solvent systems, and converts to other forms in acetone and other anhydrous systems.

5.2.3 Form C

Form C can be obtained from evaporations, slurries and slow cools in acetone solvent systems. A representative XRPD pattern of this form is shown in FIG. 12. The data are characterized by peaks at approximately 15.5 and 25 degrees 2 θ .

Solution proton NMR indicates that the 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione molecule is intact. Representative IR and Raman spectra are shown in FIGS. 13 and 14, respectively. The IR spectrum of Form C is characterized by peaks at approximately 3466, 3373, and 3318 cm⁻¹. The Raman spectrum of Form C is characterized by peaks at about 3366, 3321, 1101, and 595 cm⁻¹.

Representative thermal characteristics for Form C are plotted in FIG. 15. Form C loses about 10.02% volatiles up to about 175° C., indicating it is a solvated material. Weight loss above about 175° C. is attributed to decomposition. Identification of volatiles in Form C can be accomplished with TG-IR experiments. The representative IR spectrum captured after several minutes of heating, as depicted in FIG. 13, when compared with a spectral library, shows acetone to be the best match. Calculations from TGA data show that Form C is a hemisolvate (approximately 0.497 moles of acetone). The DSC curve for Form C, shown in FIG. 15, exhibits endotherms at about 150 and about 269° C. The endotherm at about 150° C. is attributed to solvent loss based on observations made during hot stage microscopy experiments. The endotherm at about 269° C. is attributed to the melt based on hot stage experiments.

Representative moisture sorption and desorption balance data are shown in FIG. 17. Form C does not exhibit a significant weight gain from 5 to 85% relative humidity, when

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equilibrium is obtained at each relative humidity step up to 85% relative humidity. At 95% relative humidity, Form C experiences a significant weight loss of about 6.03%. As the sample dries from 95% back down to 5% relative humidity, the sample maintains the weight achieved at the end of the adsorption phase at each step down to 5% relative humidity. Form C is capable of converting to Form B when stored at about 84% relative humidity for approximately ten days.

Interconversion studies show that Form C typically converts to Form A in a THF solvent system and typically converts to Form E in an aqueous solvent system. In an acetone solvent system, Form C is the most stable form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Desolvation experiments performed on Form C show that upon heating at about 150° C. for about five minutes, Form C will typically convert to Form A.

In sum, Form C is a crystalline, hemisolvated solid, which has a DSC thermogram exhibiting endotherms at about 150 and about 269° C. Form C is not hygroscopic below about 85% RH, but can convert to Form B at higher relative humidities.

5.2.4 Form D

Form D can be obtained from evaporation in acetonitrile solvent systems. A representative XRPD pattern of the form is shown in FIG. 18. The pattern is characterized by peaks at approximately 27 and 28 degrees 2 θ .

Solution proton NMR indicates that the 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione molecule is intact. Representative IR and Raman spectra are shown in FIGS. 19 and 20, respectively. The IR spectrum of Form D is characterized by peaks at approximately 3509, 2299, and 2256 cm⁻¹. The Raman spectrum of Form D is characterized by peaks at approximately 2943, 2889, 2297, 2260, 1646, and 1150 cm⁻¹.

Representative thermal characteristics for Form D are plotted in FIG. 21. Form D loses about 6.75% volatiles up to about 175° C., indicating a solvated material. Weight loss above about 175° C. is attributed to decomposition. TG-IR experiments indicate that the volatiles are water and acetonitrile. Calculations from TG data show that about one mole of water is present in the sample. A representative DSC curve for Form D exhibits endotherms at about 122 and about 270° C. The endotherm at about 122° C. is attributed to loss of volatiles based on observations made during hot stage microscopy experiments. The endotherm at about 270° C. is attributed to the melt based on hot stage experiments.

Representative moisture sorption and desorption data are plotted in FIG. 22. Form D does not exhibit a significant weight gain from 5 to 95% relative humidity when equilibrium is obtained at each relative humidity step. As the form dries from 95% back down to 5% relative humidity, it maintains its weight such that at 5% relative humidity the form has typically gained only about 0.39% by weight (about 0.012 mg) from start to finish. Form A is capable of converting to Form B when stored at about 84% relative humidity for approximately ten days.

Interconversion studies show that Form D is capable of converting to Form A in a THF solvent system, to Form E in an aqueous solvent system, and to Form C in an acetone solvent system. Desolvation experiments performed on Form D show that upon heating at about 150° C. for about five minutes Form D will typically convert to Form A.

In sum, Form D is a crystalline solid, solvated with both water and acetonitrile, which has a DSC thermogram exhibiting endotherms at about 122 and about 270° C. Form D is either weakly or not hygroscopic, but will typically convert to Form B when stressed at higher relative humidities.

5.2.5 Form E

Form E can be obtained by slurrying 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione in water and by a slow evaporation of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione in a solvent system with a ratio of about 9:1 acetone:water. A representative XRPD pattern is shown in FIG. 23. The data are characterized by peaks at approximately 20, 24.5 and 29 degrees 2 θ .

Representative thermal characteristics of Form E are plotted in FIG. 24. Form E typically loses about 10.58% volatiles up to about 125° C., indicating that it is a solvated material. A second weight loss of an additional about 1.38% was observed between about 125° C. and about 175° C. Weight loss above about 175° C. is attributed to decomposition. Karl Fischer and TG-IR experiments support the conclusion that the volatile weight loss in Form E is due to water. The representative DSC curve for Form E exhibits endotherms at about 99, 161 and 269° C. Based on observations made during hot stage microscopy experiments, the endotherms at about 99 and about 161° C. are attributed to loss of volatiles. The endotherm at about 269° C. is attributed to the melt based on hot stage experiments.

Representative moisture sorption and desorption data are plotted in FIG. 25. Form E typically does not exhibit a significant weight change from 5 to 95% relative humidity when equilibrium is obtained at each relative humidity step. As the sample dried from 95% back down to 5% relative humidity, the sample continues to maintain weight such that at 5% relative humidity the sample has lost only about 0.0528% by weight from start to finish.

Interconversion studies show that Form E can convert to Form C in an acetone solvent system and to Form G in a THF solvent system. In aqueous solvent systems, Form E appears to be the most stable form. Desolvation experiments performed on Form E show that upon heating at about 125° C. for about five minutes, Form E can convert to Form B. Upon heating at 175° C. for about five minutes, Form B can convert to Form F.

When stored for a period of 85 days under two different temperature/relative humidity stress conditions (room temperature/0% RH and 40° C./93% RH) Form E typically does not convert to a different form. When stored for seven days at room temperature/0% RH, Form E can convert to a new form, Form H.

5.2.6 Form F

Form F can be obtained by complete dehydration of Form E. A representative XRPD pattern of Form F, shown in FIG. 26, is characterized by peaks at approximately 19, 19.5 and 25 degrees 2 θ .

Representative thermal characteristics of Form F are shown in FIG. 27. The representative DSC curve for Form F exhibits an endotherm at about 269° C. preceded directly by two smaller endotherms indicative of a crystallized form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. The DSC thermogram does not show any thermal events prior to the melt, suggesting that it is an unsolvated material.

5.2.7 Form G

Form G can be obtained by slurrying forms B and E in THF. A representative XRPD pattern of this form, shown in FIG. 28, is characterized by a peak at approximately 23 degrees 2 θ . Two other peaks unique to Form G appear at approximately 21 and 24.5 degrees 2 θ .

Representative thermal characteristics of Form G are plotted in FIG. 29. A representative DSC curve for Form G exhibits an endotherm at about 248° C. followed by a small, broad exotherm at about 267° C. No thermal events are seen

in the DSC thermogram at lower temperatures, suggesting that it is an unsolvated material.

5.2.8 Form H

Form H can be obtained by storing Form E at room temperature and 0% RH for about 7 days. A representative XRPD pattern is shown in FIG. 30. The pattern is characterized by a peak at 15 degrees 2 θ , and two other peaks at 26 and 31 degrees 2 θ .

Representative thermal characteristics are shown in FIG. 31. Form H loses about 1.67% volatiles up to about 150° C. Weight loss above about 150° C. is attributed to decomposition. Karl Fischer data shows that Form H typically contains about 1.77% water (about 0.26 moles), suggesting that the weight loss seen in the TG is due to dehydration. The DSC thermogram shows a broad endotherm between about 50° C. and about 125° C., corresponding to the dehydration of Form H and a sharp endotherm at about 269° C., which is likely due to a melt.

When slurried in water with either Forms A or B, after about 14 days Form H can convert to Form E. When slurried in THF, Form H can convert to Form A. When slurried in acetone, Form H can convert to Form C.

In sum, Form H is a crystalline solid, hydrated with about 0.25 moles of water, which has a DSC thermogram exhibiting an endotherm between about 50 and 125° C. and an endotherm at about 269° C.

5.3 Methods of Use and Pharmaceutical Compositions

Polymorphs of the invention exhibit physical characteristics that are beneficial for drug manufacture, storage or use. All polymorphs of the invention have utility as pharmaceutically active ingredients or intermediates thereof.

This invention encompasses methods of treating and preventing a wide variety of diseases and conditions using polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. In each of the methods, a therapeutically or prophylactically effective amount of the compound is administered to a patient in need of such treatment or prevention. Examples of such disease and conditions include, but are not limited to, diseases associated with undesired angiogenesis, cancer (e.g., solid and blood borne tumors), inflammatory diseases, autoimmune diseases, and immune diseases. Examples of cancers and pre-cancerous conditions include those described in U.S. Pat. Nos. 6,281,230 and 5,635,517 to Muller et al. and in various U.S. patent applications to Zeldis, including application Ser. No. 10/411,649, filed Apr. 11, 2003 (Treatment of Myelodysplastic Syndrome); Ser. No. 10/438,213 filed May 15, 2003 (Treatment of Various Types of Cancer); Ser. No. 10/411,656, filed Apr. 11, 2003 (Treatment of Myeloproliferative Diseases). Examples of other diseases and disorders that can be treated or prevented using compositions of the invention are described in U.S. Pat. Nos. 6,235,756 and 6,114,335 to D'Amato and in other U.S. patent applications to Zeldis, including Ser. No. 10/693,794, filed Oct. 23, 2003 (Treatment of Pain Syndrome) and Ser. No. 10/699,154, filed Oct. 30, 2003 (Treatment of Macular Degeneration). The entirety of each of the patents and patent applications cited herein is incorporated herein by reference.

Depending on the disease to be treated and the subject's condition, polymorphs of the invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implantation), inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. Because individual poly-

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morphs have different dissolution, stability, and other properties, the optimal polymorph used in methods of treatment may depend on the route of administration. For example, forms that are readily soluble in aqueous solutions are preferably used to provide liquid dosage forms, whereas forms that exhibit great thermal stability may be preferred in the manufacture of solid dosage forms (e.g., tablets and capsules).

Although the physical characteristics of polymorphs can, in some cases, affect their bioavailability, amounts of the polymorphs that are therapeutically or prophylactically effective in the treatment of various disease and conditions can be readily determined by those of ordinary skill in the pharmacy or medical arts. In certain embodiments of the invention, a polymorph is administered orally and in a single or divided daily doses in an amount of from about 0.10 to about 150 mg/day, or from about 5 to about 25 mg/day. In other embodiments, a polymorph is administered every other day in an amount of from about 0.10 to about 150 mg/day, or from about 5 to about 25 mg/day.

The invention encompasses pharmaceutical compositions and single unit dosage forms that can be used in methods of treatment and prevention, which comprise one or more polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and optionally one or more excipients or diluents. Specific compositions and dosage forms are disclosed in the various patents and patent applications incorporated herein by reference. In one embodiment, a single dosage form comprises a polymorph (e.g., Form B) in an amount of about 5, 10, 25 or 50 mg.

6. EXAMPLES

6.1 Polymorph Screen

A polymorph screen to generate the different solid forms of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione was carried out as follows.

A weighed sample of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (usually about 10 mg) was treated with aliquots of the test solvent. Solvents were either reagent or HPLC grade. The aliquots were usually about 200 μ L. Between additions, the mixture was usually shaken or sonicated. When the solids dissolved, as judged by visual inspection, estimated solubilities were calculated. Solubilities were estimated from these experiments based on the total solvent used to provide a solution. Actual solubilities may have been greater than those calculated due to the use of too-large solvent aliquots or to a slow rate of dissolution.

Samples were created by generating solutions (usually about 30 mg in 20 mL) at elevated temperatures, filtering, and allowing the solution to evaporate whether in an open vial (hot fast evaporation) or in a vial covered with aluminum foil containing pinholes (hot slow evaporation).

Slurry experiments were also performed. Usually about 25 mg of solid was placed in either 3 or 5 mL of solvent. The samples were then placed on orbital shakers at either ambient temperature or 40° C. for 4-10 days.

Crystallizations were performed using various cooling methods. Solid was dissolved in a solvent at an elevated temperature (e.g., about 60° C.), filtered quickly and allowed to cool to room temperature. Once at room temperature, samples that did not crystallize were moved to a refrigerator. Solids were removed by filtration or decantation and allowed to dry in the air. Crash cools were performed by dissolving solid in a solvent at an increased temperature (e.g., about 45-65° C.) followed by cooling in a dry ice/acetone bath.

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Hygroscopicity studies were performed by placing portions of each polymorph in an 84% relative humidity chamber for approximately one week.

Desolvation studies were carried out by heating each polymorph in a 70° C. oven for approximately one week.

Interconversion experiments were carried out by making slurries containing two forms in a saturated solvent. The slurries were agitated for approximately 7-20 days at ambient temperature. The insoluble solids were recovered by filtration and analyzed using XRPD.

6.2 Preparation of Polymorphic Forms

Eight solid forms of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione were prepared as described below.

Form A was obtained by crystallization from various non-aqueous solvents including 1-butanol, butyl acetate, ethanol, ethyl acetate, methanol, methyl ethyl ketone, and tetrahydrofuran. Form B was also obtained by crystallization from the solvents hexane, toluene and water. Form C was obtained from evaporations, slurries, and slow cools in acetone solvent systems. Form D was obtained from evaporations in acetonitrile solvent systems. Form E was obtained most readily by slurrying 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in water. Form F was obtained by complete desolvation of Form E. It is found to be an unsolvated, crystalline material that melts at about 269° C. Form G was obtained by slurrying forms B and E in THF. Form H was obtained by stressing Form E at room temperature and 0% RH for 7 days.

6.2.1 Synthesis of Polymorphs B and E

Form B is the desired polymorph for the active pharmaceutical ingredient (API) of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. This form has been used in the formulation of API into drug product for clinical studies. Three batches were produced as apparent mixtures of polymorphs in the non-micronized API of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

Development work was carried out to define a process that would generate polymorph B from this mixture of polymorphs and could be implemented for strict polymorphic controls in the validation batches and future manufacturing of API of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. Characterization of polymorphic forms produced during the work was performed by XRPD, DSC, TGA and KF.

A process was also developed for the large-scale preparation of Form E. Polymorph E material was prepared in order to carry out a comparison with polymorph B drug product in capsule dissolution testing of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. 150 g of a mixture of polymorphs in 3 L of water was stirred at room temperature for 48 hours. The product was collected by filtration and dried at 25° C. for 24 hours under vacuum. XRPD, DSC, TGA, KF and HPLC analyses confirmed that the material isolated was polymorph E.

In a preliminary work, it was demonstrated that stirring a suspension of a mixture of polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione with water at high temperature (75° C.) for an extended period of time converted this mixture of polymorphs exclusively to form B. Several specific parameters were identified including temperature, solvent volume and drying parameters (temperature and vacuum). XRPD, DSC, TGA, KF and HPLC analyses were used to characterize all of the batches. After completing the optimization work, the optimized process was scaled-up to 100-200 g on three lots of API. Drying studies were carried

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out at 20° C., 30° C. and 40° C., and 65° C. with a vacuum of 150 mm of Hg. The results are shown in Tables 1-5.

The cooling and holding periods of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione slurry were studied. The experimental laboratory data suggests that polymorph B seems to be forming first, and overtime equilibration to polymorph E at RT conditions occurs, therefore generating a mixture of polymorphs B and E. This result supports the fact that polymorph B seems to be a kinetic product, and that prolonged processing time converts the material to polymorph E resulting in a mixture of polymorphs B and E.

A laboratory procedure was developed to exclusively produce polymorph B of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. The procedure includes a stirred 10 volume water slurry at ~75° C. for 6-24 hours. The following preferred process parameters have been identified:

1. Hot slurry temperature of 70-75° C.
2. Product filtration of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione at 65-75° C.
3. Drying under vacuum at 60-70° C. is preferred for an efficient removal of unbound water in 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione wet cake.
4. The filtration step of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione may be a time sensitive operation. The use of efficient solid-liquid separation equipment is preferred.
5. Holding periods of water-wet cake of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione at KF higher than 5% may cause the kinetic equilibrations of polymorph B to mixed polymorphs of E and B.

Drying to KF <4.0% water was achieved in ~3 hours (30-70° C., 152 mm Hg). Polymorphs B and E were distinguished by the water levels as measured by KF and TGA. The reference sample of polymorph B is micronized API. In order to make accurate comparison by XRPD samples were gently grinded before submission for analysis. This increases the clarity of the identification of the polymorphic form. All samples were analyzed for XRPD, DSC, TGA, KF and HPLC.

TABLE 1

Preliminary Studies			
Amount	Reaction conditions	Analysis	Results/conclusion
2 g	Water, rt, 48 h	XRPD, DSC, TGA, KF	Polymorph E
25 g	Water, rt, 48 h	XRPD, DSC, TGA, KF	Polymorph E
5 g	Water, 70-75° C., 24 h then rt 24 h	XRPD, DSC, TGA, KF	Polymorph B
1 g	9:1 Acetone - water, Slow evpo. 175° C. 1 h in an oven	XRPD, DSC, TGA, KF	Polymorph Mixture
1 g	Water, rt, 24 h	XRPD, DSC, TGA, KF	Polymorph A
0.5 g (polymorph A)	Water, rt, 48 h	XRPD, DSC, TGA, KF	Polymorph E
1 g polymorph B	Water, 70-75° C., 24 h	XRPD, DSC, TGA, KF	Polymorph B
1 g polymorph E	Slurry in heptane	XRPD, DSC, TGA, KF	No change

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TABLE 2

Optimization of Temperature, Time and Solvent Volume				
Amount	Amount Water (mL)	Temp (° C.)	Time (h)	Results/conclusion
10 g	50	75	6	Mix
10 g	50	75	24	Polymorph B
10 g	100	70	6	Polymorph B
10 g	100	70	14	Polymorph B
10 g	100	70	21	Polymorph B
10 g	100	75	6	Polymorph B
10 g	100	75	24	Polymorph B
10 g	100	75	6	Polymorph B
10 g	100	75	19	Polymorph B
10 g	100	75	14	Polymorph B
10 g	100	75	24	Polymorph B
5 g	100	75	18	Polymorph B
10 g	100	80	6	Polymorph B
10 g	100	80	20	Polymorph B
10 g	200	45	6	Polymorph B + E
10 g	200	45	24	Polymorph E
10 g	200	60	48	Polymorph B
10 g	200	75	6	Mix
10 g	200	75	24	Polymorph B
10 g	200	75	13	Polymorph B
10 g	200	75	24	Polymorph B

Optimum conditions were determined to be 10 volumes of solvent (H₂O), 70-80° C. for 6-24 hours.

TABLE 3

Holding Time				
Amount	Reaction Conditions	Holding Time (h)	Holding Temp (° C.)	Results/Conclusion
5 g	Water, 70-75° C., 24 h	24	23-25	Polymorph B
1 g	Water, 70-75° C., 24 h	48	23-25	Polymorph E
Polymorph B				
2 g	Water, 40 mL	16	23-25	Polymorph E
150 g	Water, 3.0 L	24	23-25	Polymorph E
150 g	Water, 3.0 L	48	23-25	Polymorph E
10 g	Water, 100 mL, 24 h, 75° C.	18	23-25	Polymorph B
10 g	Water, 100 mL, 24 h, 75° C.	18	40	Polymorph B
10 g	Water, 200 mL, 24 h, 75° C.	14	-5	Mix
10 g	Water, 200 mL, 24 h, 75° C.	14	23-25	Polymorph E
10 g	Water, 200 mL, 24 h, 75° C.	14	40	Mix
10 g	Water, 100 mL, 24 h, 75° C.	21	23-25	Polymorph E
10 g	Water, 100 mL, 24 h, 75° C.	21	40	Mix
10 g	Water, 100 mL, 14 h, 75° C.	2	23-25	Mix

Holding time gave mixed results and it was determined that the material should be filtered at 60-65° C. and the material washed with 0.5 volume of warm (50-60° C.) water.

TABLE 4

Scale-up Experiments				
Amount	Amount Water (L)	Temp (° C.)	Time (h)	Results/Conclusion
100 g	1.0	75	6	Polymorph B
100 g	1.0	75	22	Polymorph B

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TABLE 4-continued

Scale-up Experiments				
Amount	Amount Water (L)	Temp (° C.)	Time (h)	Results/ Conclusion
100 g	1.0	75	6	Polymorph B
100 g	1.0	75	24	Polymorph B
100 g	1.0	75	6	Polymorph B
100 g	1.0	75	22	Polymorph B

TABLE 5

Drying Studies					
Amount	Drying Time (h)	Drying Temp (° C.)	Vacuum (mm Hg)	KF§ (%)	Results/ Conclusion
100 g	0	—	—	3.690	Polymorph B
100 g	3	30	152	3.452	Polymorph B
100 g	8	30	152	3.599	Polymorph B
100 g	0	—	—	3.917	Polymorph B
100 g	5	40	152	3.482	Polymorph B
100 g	22	40	152	3.516	Polymorph B
100 g	3	40	152	3.67	Polymorph B
100 g	22	40	152	3.55	Polymorph B

* Reaction Conditions: Water 1 L, 75° C., 22-24 h;

§ Average of 2 runs.

Drying studies determined that the material should be dried at 35-40° C., 125-152 mm Hg for 3 to 22 h or until the water content reaches $\leq 4\%$ w/w.

For a large scale preparation of polymorph E (5222-152-B), a 5-L round bottom flask was charged with 3-(4-amino-1-oxo-1,3 dihydro-isoinol-2-yl)-piperidine-2,6-dione (150 g, 0.579 mol) and water (3000 mL, 20 vol). The mixture was mechanically stirred at room temperature (23-25° C.) for 48 h under nitrogen atmosphere.

Samples were taken after 24 h and 48 h before the mixture was filtered and air-dried on the filter for 1 h. The material was transferred to a drying tray and dried at room temperature (23-25° C.) for 24 h. KF analysis on the dried material showed water content of 11.9%. The material was submitted for XRPD, TGA, DSC and HPLC analysis. Analysis showed the material was pure polymorph E.

For a large scale preparation of polymorph B (5274-104), a 2 L-3-necked round bottom flask was charged with 3-(4-amino-1-oxo-1,3 dihydro-isoinol-2-yl)-piperidine-2,6-dione (polymorph mixture, 100 g, 0.386 mol) and water (1000 mL, 10.0 vol). The mixture was heated to 75° C. over approximately 30 minutes with mechanical stirring under nitrogen atmosphere.

Samples were taken after 6 h and 24 h before the mixture was allowed to cool to 60-65° C., filtered and the material washed with warm (50-60° C.) water (50 mL, 0.5 vol). The material was transferred to a drying tray and dried at 30° C., 152 mm Hg for 8 h. KF analysis on the dried material showed water content of 3.6%. After grinding the material was submitted for XRPD, TGA, DSC and HPLC analysis. Analysis showed the material was pure polymorph B. The results of the analyses are shown in FIGS. 32-46.

6.3 X-Ray Powder Diffraction Measurements

X-ray powder diffraction analyses were carried out on a Shimadzu XRD-6000 X-ray powder diffractometer using Cu K α radiation. The instrument is equipped with a fine-focus X-ray tube. The tube voltage and amperage were set at 40 kV and 40 mA, respectively. The divergence and scattering slits were set at 1° and the receiving slit was set at 0.15 mm.

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Diffacted radiation was detected by a NaI scintillation detector. A theta-two theta continuous scan at 3°/min (0.4 sec/0.02° step) from 2.5 degrees 2 θ to 40 degrees 2 θ was used. A silicon standard was analyzed each day to check the instrument alignment.

X-ray powder diffraction analyses were also carried out using Cu K α radiation on an Inel XRG-3000 diffractometer equipped with a curved position-sensitive detector. Data were collected in real time over a theta-two theta range of 120° at a resolution of 0.030°. The tube voltage and current were 40 kV and 30 mA, respectively. A silicon standard was analyzed each day to check for instrument alignment. Only the region between 2.5 and 40 degrees 2 θ is shown in the figures.

6.4 Thermal Analysis

TG analyses were carried out on a TA Instrument TGA 2050 or 2950. The calibration standards were nickel and alumel. Approximately 5 mg of sample was placed on a pan, accurately weighed, and inserted into the TG furnace. The samples were heated in nitrogen at a rate of 10° C./min, up to a final temperature of 300 or 350° C.

DSC data were obtained on a TA 2920 instrument. The calibration standard was indium. Approximately 2-5 mg samples were placed into a DSC pan and the weight accurately recorded. Crimped pans with one pinhole were used for analysis and the samples were heated under nitrogen at a rate of 10° C./min, up to a final temperature of 350° C.

Hot-stage microscopy was carried out using a Kofler hot stage mounted on a Leica Microscope. The instrument was calibrated using USP standards.

A TA Instruments TGA 2050 interfaced with a Nicolet model 560 Fourier transform IR spectrophotometer, equipped with a globar source, XT/KBr beamsplitter, and deuterated triglycine sulfate (DTGS) detector, was utilized for TG-IR experiments. The IR spectrometer was wavelength calibrated with polystyrene on the day of use while the TG was temperature and weight calibrated biweekly, using indium for the temperature calibration. A sample of approximately 10 mg of 3-(4-amino-1-oxo-1,3 dihydro-isoinol-2-yl)-piperidine-2,6-dione was weighed into an aluminum pan and heated from 25 to 30° C. to 200° C. at a rate of 20° C./min with a helium purge. IR spectra were obtained in series, with each spectrum representing 32 co-added scans at a resolution of 4 cm⁻¹. Spectra were collected with a 17-second repeat time. TG/IR analysis data are presented as Gram-Schmidt plots and IR spectra linked to the time. Gram-Schmidt plots show total IR intensity vs. time; hence, the volatiles can be identified at each time point. They also show when the volatiles are detected. From the Gram-Schmidt plots, time points were selected and the IR spectra of these time points are presented in the stacked linked spectra. Each spectrum identifies volatiles evolving at that time point. Volatiles were identified from a search of the HR Nicolet TGA vapor phase spectral library. The library match results are also presented to show the identified vapor.

6.5 Spectroscopy Measurements

Raman spectra were acquired on a Nicolet model 750 Fourier transform Raman spectrometer utilizing an excitation wavelength of 1064 nm and approximately 0.5 W of Nd:YAG laser power. The spectra represent 128 to 256 co-added scans acquired at 4 cm⁻¹ resolution. The samples were prepared for analysis by placing the material in a sample holder and positioning this in the spectrometer. The spectrometer was wavelength calibrated using sulfur and cyclohexane at the time of use.

The mid-IR spectra were acquired on a Nicolet model 860 Fourier transform IR spectrophotometer equipped with a glo-

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bar source XT/KBr beamsplitter and a deuterated triglycine sulfate (DTGS) detector. A Spectra-Tech, Inc. diffuse reflectance accessory was utilized for sampling. Each spectrum represents 128 co-added scans at a spectral resolution of 4 cm^{-1} . A background data set was acquired with an alignment mirror in place. A single beam sample data set was then acquired. Subsequently, a log 1/R (where R=reflectance) spectrum was acquired by rationing the two data sets against each other. The spectrophotometer was calibrated (wavelength) with polystyrene at the time of use.

6.6 Moisture Sorption/Desorption Measurements

Moisture sorption/desorption data were collected on a VTI SGA-100 moisture balance system. For sorption isotherms, a sorption range of 5 to 95% relative humidity (RH) and a desorption range of 95 to 5% RH in 10% RH increments was used for analysis. The sample was not dried prior to analysis. Equilibrium criteria used for analysis were less than 0.0100 weight percent change in 5 minutes with a maximum equilibration time of 3 hours if the weight criterion was not met. Data were not corrected for the initial moisture content of the samples.

6.7 Solution Proton NMR Measurements

NMR spectra not previously reported were collected at SSCI, Inc, 3065 Kent Avenue, West Lafayette, Ind. Solution phase ^1H NMR spectra were acquired at ambient temperature on a Bruker model AM spectrometer. The ^1H NMR spectrum represents 128 co-added transients collected with a 4 μsec pulse and a relaxation delay time of 5 seconds. The free induction decay (FID) was exponentially multiplied with a 0.1 Hz Lorentzian line broadening factor to improve the signal-to-noise ratio. The NMR spectrum was processed utilizing GRAMS software, version 5.24. Samples were dissolved in dimethyl sulfoxide- d_6 .

The scope of this invention can be understood with reference to the appended claims.

6.8 Intrinsic Dissolution and Solubility Studies

Intrinsic dissolution experiments were conducted on Form A (anhydrous), Form B (hemihydrate), and Form E (dihydrate) of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Equilibrium solubility experiments were conducted on Forms A and B. Aliquots were analyzed by ultraviolet-visible spectrophotometry, and the solids remaining from each experiment were analyzed by X-ray powder diffraction (XRPD).

6.8.1 Experimental

6.8.1.1 Dissolution

Dissolution experiments were carried out in a VanKel VK6010-8 dissolution apparatus equipped with a VK650A heater/circulator. An intrinsic dissolution apparatus (Woods apparatus) was used. Samples were compressed at 1.5 metric tons (1000 psi) for 1 min using the Woods apparatus in a hydraulic press, giving a sample surface of 0.50 cm^2 . A dissolution medium consisting of 900 mL HCl buffer, pH 1.8, with 1% sodium lauryl sulfate, was used for each experiment. The medium was degassed by vacuum filtration through a 0.22- μm nylon filter disk and maintained at 37° C. The apparatus was rotated at 50 rpm for each experiment. Aliquots were filtered immediately using 0.2- μm nylon syringe filters. In some cases, the undissolved solids were recovered and analyzed by X-ray powder diffraction (XRPD).

6.8.1.2 Solubility

Equilibrium solubility experiments were conducted in a 100-mL, three-neck, round-bottom flask immersed in a constant temperature oil bath maintained at 25° C. A solid sample of 400-450 mg was stirred in 50 mL of dissolution medium (HCl buffer, pH 1.8, with 1% sodium lauryl sulfate) using a mechanical stir rod. Aliquots were filtered using 0.2- μm

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nylon syringe filters and immediately diluted 1 mL→50 mL, then 5 mL→25 mL with dissolution medium in Class A glassware, a final dilution factor of 250.

6.8.1.3 UV-Vis Spectrophotometry

Dissolution and solubility samples solutions were analyzed by a Beckman DU 640 single-beam spectrophotometer. A 1.000-cm quartz cuvette and an analysis wavelength of 228.40 nm were utilized. The detector was zeroed with a cuvette filled with dissolution medium.

6.8.1.4 X-Ray Powder Diffraction

XRPD analyses were carried out on a Shimadzu XRD-6000 X-ray powder diffractometer using Cu K α radiation. The instrument is equipped with a fine focus X-ray tube. The tube power and amperage were set at 40 kV and 40 mA, respectively. The divergence and scattering slits were set at 1° and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. A theta-two theta continuous scan at 3°/min (0.4 sec/0.02° step) from 2.5 to 40° 2 θ was used. A silicon standard was analyzed each day to check the instrument alignment. Samples were packed in an aluminum holder with silicon insert.

6.8.2 Results

The results of these solubility and intrinsic studies are summarized in Table 6. Both the solubility and dissolution experiments were conducted in a medium of HCl buffer, pH 1.8, containing 1% sodium lauryl sulfate. Form A was found to be unstable in the medium, converting to Form E. The solubilities of Forms A, B, and E were estimated to be 6.2, 5.8, and 4.7 mg/mL, respectively. The dissolution rates of Forms A, B, and E were estimated to be 0.35, 0.34, and 0.23 mg/mL, respectively.

6.8.2.1 UV-Vis Spectrophotometry Method Development

A UV-Vis scan of the dissolution medium (blanked with an empty cuvette) was done to identify any interfering peaks. A small peak at 225 nm was present as shown in FIG. 47.

Solutions of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione at varying concentrations were analyzed by UV-Vis spectrophotometry. A preliminary scan of a 1.0 mg/mL solution was done, with the instrument blanked with dissolution medium. The solution was highly absorbing and noisy from 200-280 nm, making dilution necessary.

A 0.04 mg/mL solution of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione was then scanned from 200-300 nm. The plot was still noisy between 200 and 230 nm as shown in FIG. 48. The sample was further diluted to 0.008 mg/mL. A wavelength scan of 200-350 nm for this sample showed a peak at 228.4 nm with no interference, as shown in FIG. 49. Therefore, a wavelength of 228.4 was chosen for analysis of the solubility and dissolution samples.

A six-point calibration curve was generated with standards of the following concentrations: 0.001 mg/mL, 0.002 mg/mL, 0.005 mg/mL, 0.010 mg/mL, 0.015 mg/mL, and 0.020 mg/mL (Notebook 569-90). A linearity coefficient of $R^2=0.9999$ was obtained as shown in FIG. 50.

6.8.2.2 Solubility

A sample consisting of 449.4 mg Form A was slurried in dissolution medium. Particle size was not controlled. Aliquots were taken at 7, 15, 30, 60, 90, and 150 min. The concentration reached 6.0 mg/mL by the first time point. The highest concentration reached was 6.2 mg/mL, at 30 min. From that point the concentration decreased, reaching 4.7 mg/mL at 150 min as in FIG. 51. The solids remaining at the final time point were analyzed by XRPD and found to be Form E as shown in Table 7. No peaks attributed to Form A can be seen in the pattern. Since the concentration did not plateau at 4.7 mg/mL, the solubility of Form E may be lower than that.

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A sample consisting of 401.4 mg Form B was slurried in dissolution medium. Particle size was not controlled. Aliquots were taken at 7, 15, 30, 60, 90, 180, 420, and 650 min. Form B dissolved much more slowly than Form A, reaching 3.3 mg/mL in 90 min. The concentration stabilized at 5.6-5.7 mg/mL at the final three time points as in FIG. 52. The remaining solids were shown to be Form B as in Table 7, suggesting Form B has good stability in water.

A summary of the solubilities is given in Table 6. The amounts dissolved at each time point are shown in Tables 8 and 9.

TABLE 6

<u>Summary of Results</u>				
Form	Solubility	Intrinsic Dissolution #1	Intrinsic Dissolution #2	Average Intrinsic Dissolution Rate
Form A	6.2 mg/mL	0.35	0.22 ^a	0.29 ^a
Form B	5.8 mg/mL	0.35	0.32	0.34
Form E	4.7 mg/mL	0.21	0.25	0.23

^aThe Form A dissolution experiment #2 may have converted to Form E on the surface of the disk, skewing the average rate lower.

TABLE 7

<u>Experimental Details</u>		Final Form
Experiment		
Pressed Form A		A
Pressed Form B		B
Form A Solubility		E
Form B Solubility		B
Form A Dissolution		—
Form A Dissolution		A
Form B Dissolution		—
Form B Dissolution		B
Form E Dissolution		E
Form E Dissolution		—

TABLE 8

<u>Form A Solubility</u>	
Time Point (min)	Concentration (mg/mL)
7	6.00
15	6.11
30	6.16
60	6.10
90	5.46
150	4.73

TABLE 9

<u>Form B Solubility</u>	
Time Point (min)	Concentration (mg/mL)
7	1.63
15	2.14
30	2.33
60	2.94
90	3.34
180	5.67
420	5.76
650	5.61

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6.8.2.3 Intrinsic Dissolution

Approximately 200 mg each of Forms A and B were compressed into disks in the Woods apparatus using 2 metric tons of pressure. The samples were subsequently scraped out, ground gently, and analyzed by XRPD. The study showed that compression and grinding does not cause a form change in either case. (See Table 7).

Two preliminary dissolution runs were performed. The disks fractured to some extent in both experiments, compromising the requirement of constant surface area.

The first experiment of intrinsic dissolution that strictly followed the USP chapter on intrinsic dissolution utilized approximately 150 mg each of Forms A and B. Seven aliquots, beginning at 5 min and ending at 90 min, were taken to maintain sink conditions. The experiment resulted in linear dissolution profiles, with a rate of 0.35 mg per cm² per minute for both forms. The Form E experiment was done later under the same conditions and added to the graph for comparison. (See FIG. 53). The Form E dissolution rate was 0.21 mg per cm² per minute, significantly lower than the dissolution rate of Forms A and B. This is in line with expectations based on the solubility data. The crystal form of the remaining solids did not change in any case.

The second experiment utilized approximately 250 mg each of Forms A and B. The Form E experiment (135 mg) was done later and added to the graph for comparison. (See FIG. 54). Nine aliquots were taken, beginning at 5 min and ending at 150 min. The dissolution rates were 0.22, 0.32, and 0.25 mg per cm² per minute, respectively, for Forms A, B, and E. The dissolution rate for Form A in this experiment was low, while the rates for Forms B and E were similar to those found in the first experiment. It is believed that in this case, a thin layer of the Form A sample disk may have converted to Form E upon exposure to water. This is supported by the evidence of rapid conversion of Form A to Form E in the solubility experiment. The diffraction pattern of the undissolved solids does not indicate a form change. However, the bulk of the sample disk is not exposed to water. Therefore, the true intrinsic dissolution rate of Form A is believed to be close to 0.35 mg per cm² per minute. An insufficient quantity of Form A was available to repeat the experiment.

A summary of the intrinsic dissolution rates is given in Table 6. The amounts dissolved at each time point are summarized in Tables 10 and 11.

TABLE 10

<u>Intrinsic Dissolution Experiment #1 Results</u>				
Time Point	Form A ^a	Form B ^a	Form E ^a	
5 min	5.76	10.80 ^b	2.70	
10 min	7.73	6.85	4.13	
20 min	11.31	10.25	6.96	
30 min	15.59	14.35	9.60	
45 min	21.98	20.57	12.57	
60 min	27.11	25.70	15.16	
90 min	34.17	34.34	20.82	

^aResults are reported as Cumulative Amount Dissolved per Unit Area (mg/cm²)

^bThis date point not included in graph since the value is higher than the next two data points.

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TABLE 11

Intrinsic Dissolution Experiment #2 Results			
Time Point	Form A ^a	Form B ^a	Form E ^a
5 min	4.50	5.04	3.06
10 min	5.22	6.12	4.31
20 min	7.54	7.73	11.40
30 min	11.46	12.72	11.93
45 min	15.01	17.33	14.72
60 min	18.38	21.93	18.52
90 min	24.38	31.64	26.24
120 min	30.35	41.31	33.56
150 min	35.26	49.54	40.82

^aResults are reported as Cumulative Amount Dissolved per Unit Area (mg/cm²)

6.9 Analyses of Mixtures of Polymorphs

This invention encompasses mixtures of different polymorphs. For example, an X-ray diffraction analysis of one production sample yielded a pattern that contained two small peaks seen at approximately 12.6° and 25.8° 2θ in addition to those representative of Form B. In order to determine the composition of that sample, the following steps were performed:

- 1) Matching of the new production pattern to known forms along with common pharmaceutical excipients and contaminants;
- 2) Cluster analysis of the additional peaks to identify if any unknown phase is mixed with the original Form B;
- 3) Harmonic analysis of the additional peaks to identify if any preferred orientation may be present or if any changes in the crystal habit may have occurred; and
- 4) Indexing of the unit cells for both Form B and the new production sample to identify any possible crystallographic relationships.

Based on these tests, which can be adapted for the analysis of any mixture of polymorphs, it was determined that the sample contained a mixture of polymorph forms B and E.

6.10 Dosage Form

Table 12 illustrates a batch formulation and single dosage formulation for a 25 mg single dose unit of a polymorphic form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione.

TABLE 12

Formulation for a 25 mg capsule			
Material	Percent By Weight	Quantity (mg/tablet)	Quantity (kg/batch)
Polymorphic Form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione	40.0%	25 mg	16.80 kg
Pregelatinized Corn Starch, NF	59.5%	37.2 mg	24.99 kg
Magnesium Stearate	0.5%	0.31 mg	0.21 kg
Total	100.0%	62.5 mg	42.00 kg

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The pregelatinized corn starch (SPRESS B-820) and polymorphic form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione components are passed through a screen (i.e., a 710 μm screen) and then loaded into a Diffusion Mixer with a baffle insert and blended for about 15 minutes. The magnesium stearate is passed through a screen (i.e., a 210 μm screen) and added to the Diffusion Mixer. The blend is then encapsulated in capsules using a Dosator type capsule filling machine.

- 10 The entire scope of this invention is not limited by the specific examples described herein, but is more readily understood with reference to the appended claims.

What is claimed is:

- 15 1. Crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione hemihydrate.

2. The hemihydrate of claim 1 having an X-ray powder diffraction pattern comprising peaks at approximately 16, 22 and 27 degrees 2θ.

- 20 3. The hemihydrate of claim 2 wherein the pattern further comprises a peak at approximately 18 degrees 2θ.

4. The hemihydrate of claim 1 having an X-ray powder diffraction pattern comprising peaks at 15.8, 22.2 and 26.7 degrees 2θ.

- 25 5. The hemihydrate of claim 4 wherein the pattern further comprises a peak at 18.2 degrees 2θ.

6. The hemihydrate of claim 1 having an X-ray powder diffraction pattern corresponding to the representative X-ray powder diffraction patterns depicted in FIG. 6, FIG. 32, FIG. 33 and FIG. 34.

- 30 7. The hemihydrate of claim 1 having a differential scanning calorimetry thermogram comprising an endotherm with a maximum at about 268° C.

8. The hemihydrate of claim 7 wherein the thermogram further comprises an endotherm corresponding to dehydration.

- 35 9. The hemihydrate of claim 1 having a differential scanning calorimetry thermogram corresponding to the representative differential scanning calorimetry thermograms depicted in FIG. 9, FIG. 42, FIG. 43 and FIG. 44.

40 10. The hemihydrate of claim 1 having between approximately 0.46 and approximately 0.59 moles of water per mole of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione.

- 45 11. The hemihydrate of claim 1 having a thermogravimetric analysis thermogram comprising a weight loss of between about 3.1% and about 4.0% when heated from about 30° C. to about 175° C.

12. The hemihydrate of claim 1 having an infrared spectrum comprising peaks at approximately 3513 and 1960 cm⁻¹.

- 50 13. The hemihydrate of claim 1 having an infrared spectrum corresponding to the representative infrared spectrum depicted in FIG. 7.

55 14. The hemihydrate of claim 1 having a Raman spectrum corresponding to the representative Raman spectrum depicted in FIG. 8.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,465,800 B2
APPLICATION NO. : 10/934863
DATED : December 16, 2008
INVENTOR(S) : Jaworsky et al.

Page 1 of 11

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Please replace Drawing Sheets 15, 26, 31, 32, 33, 35, 36, 38, 39, and 40 (of 48) with the Replacement Drawing Sheets on the following pages of this Certificate of Correction:

Page 2 of 11: Replacement Drawing Sheet 15 of 48 (Fig. 15);

Page 3 of 11: Replacement Drawing Sheet 26 of 48 (Fig. 26);

Page 4 of 11: Replacement Drawing Sheet 31 of 48 (Fig. 31);

Page 5 of 11: Replacement Drawing Sheet 32 of 48 (Figs. 32 and 33);

Page 6 of 11: Replacement Drawing Sheet 33 of 48 (Figs. 34 and 35);

Page 7 of 11: Replacement Drawing Sheet 35 of 48 (Figs. 37 and 38);

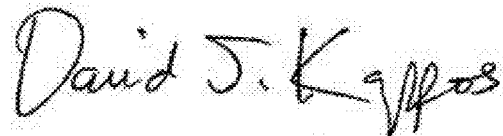
Page 8 of 11: Replacement Drawing Sheet 36 of 48 (Figs. 39 and 40);

Page 9 of 11: Replacement Drawing Sheet 38 of 48 (Figs. 42 and 43);

Page 10 of 11: Replacement Drawing Sheet 39 of 48 (Figs. 44 and 45);

Page 11 of 11: Replacement Drawing Sheet 40 of 48 (Fig. 46).

Signed and Sealed this
Nineteenth Day of April, 2011

A handwritten signature in black ink that reads "David J. Kappos". The signature is written in a cursive, flowing style.

David J. Kappos
Director of the United States Patent and Trademark Office

CERTIFICATE OF CORRECTION (continued)

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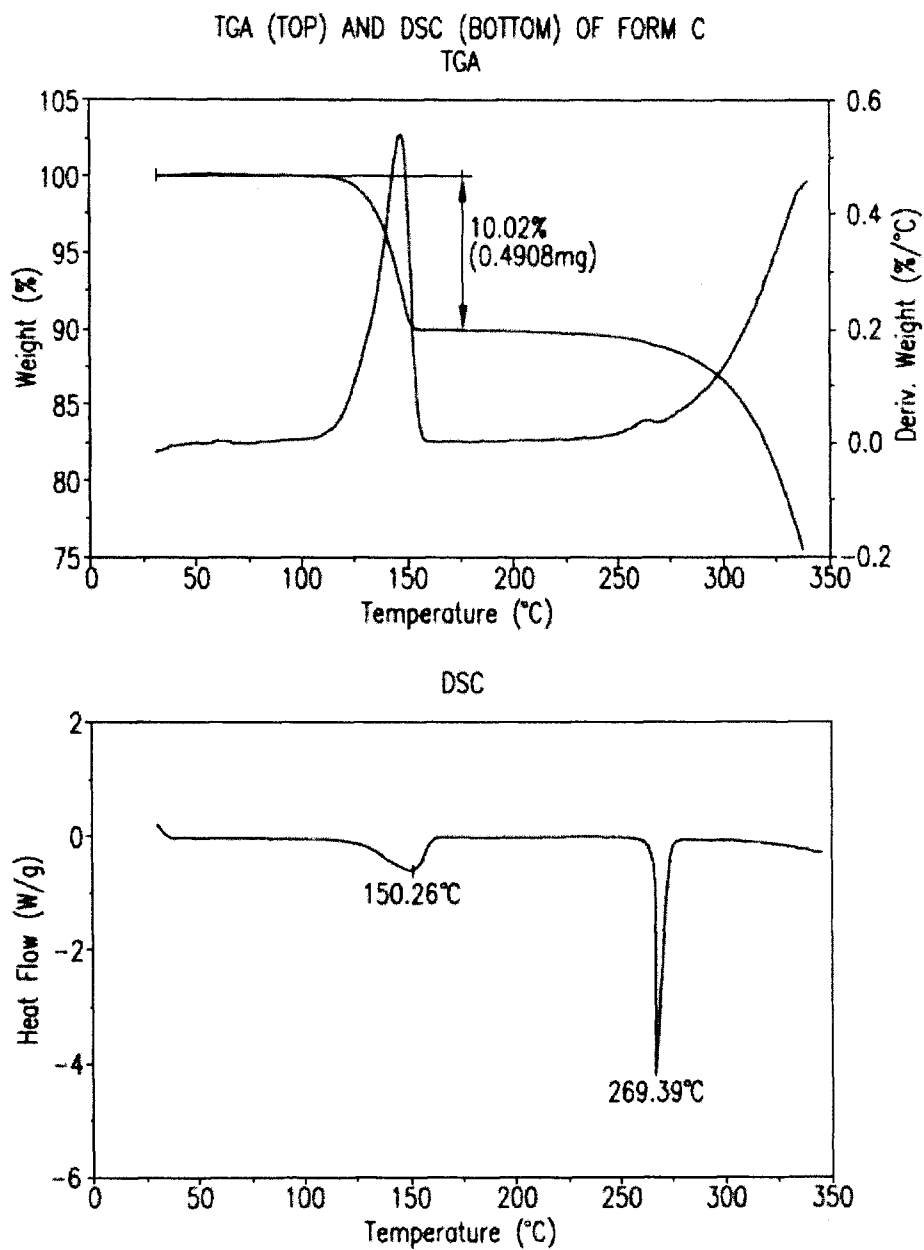


FIG.15

CERTIFICATE OF CORRECTION (continued)

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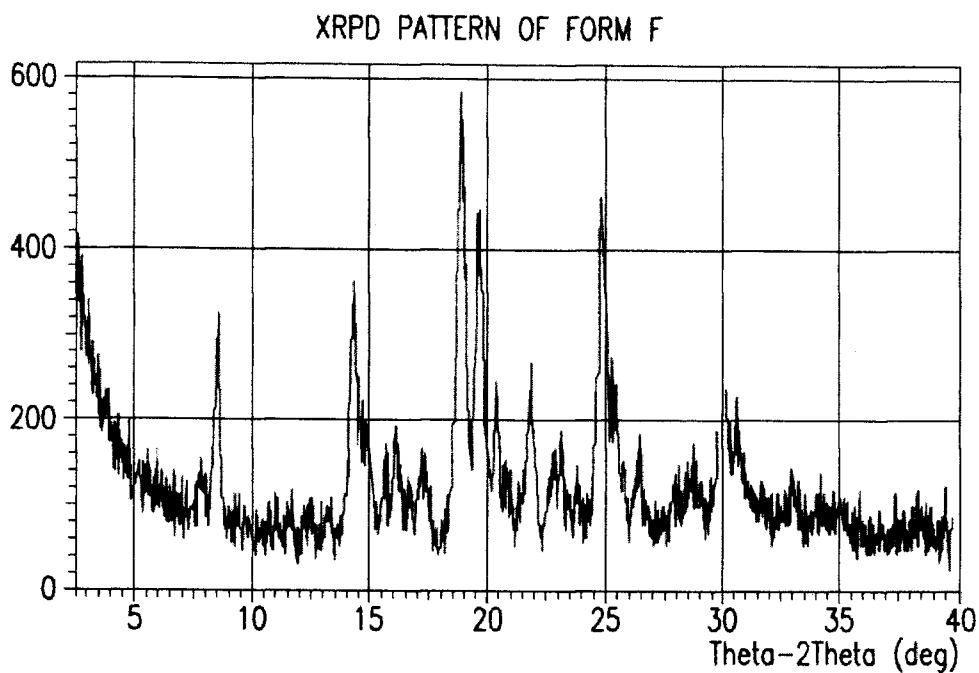


FIG.26

CERTIFICATE OF CORRECTION (continued)

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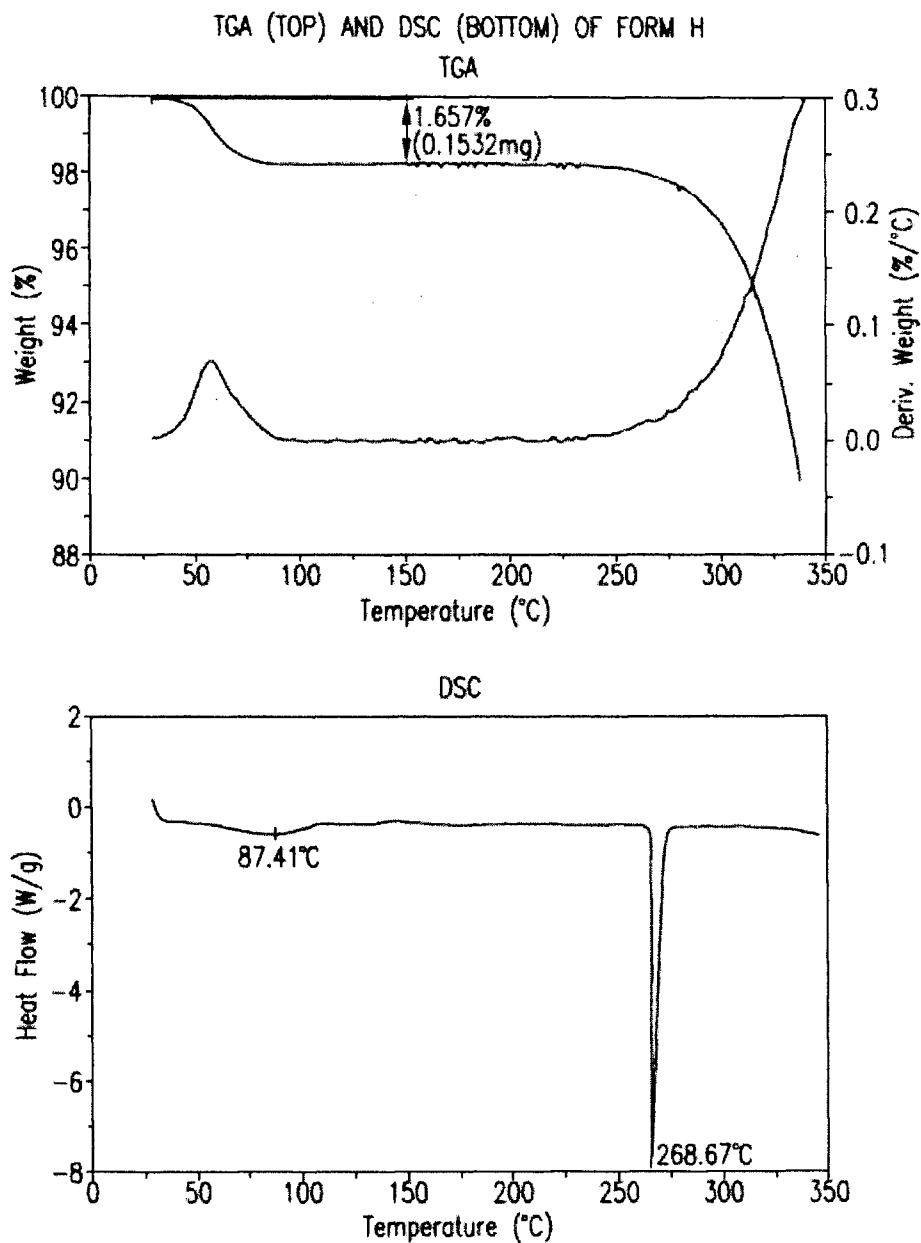


FIG.31

CERTIFICATE OF CORRECTION (continued)

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XRPD PATTERN OF POLYMORPH B

File: Process 5274-104-B

Date: 06-04-04 16:10 Step: 0.020° Cnt Time: 0.500 Sec.

Range: 1.50-40.00 (Deg) Step Scan Rate: 2.40 Deg/min.

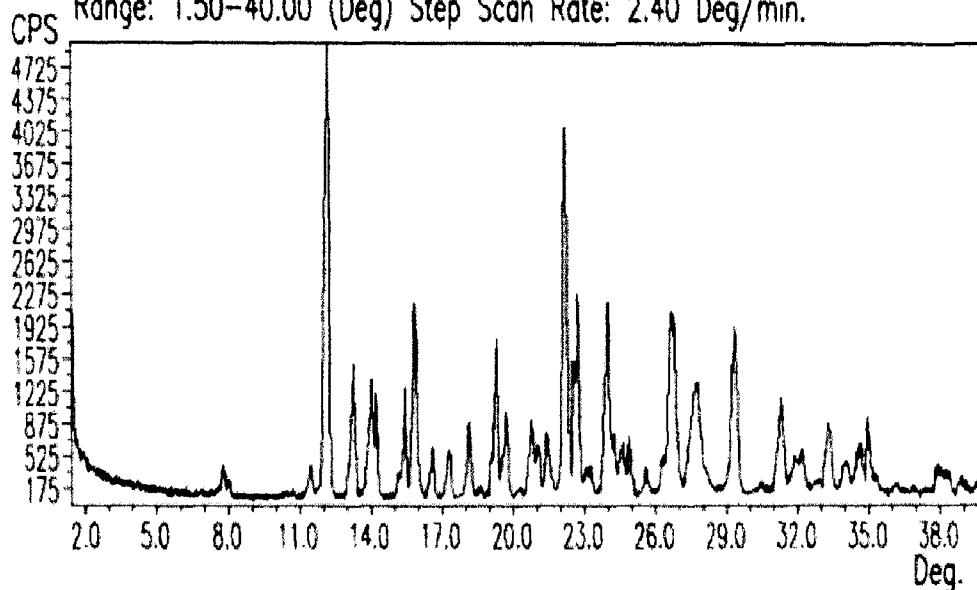


FIG.32

XRPD PATTERN OF POLYMORPH B

File: Process 5274-100-C

Date: 06-02-04 16:11 Step: 0.020° Cnt Time: 0.500 Sec.

Range: 1.50-40.00 (Deg) Step Scan Rate: 2.40 Deg/min.

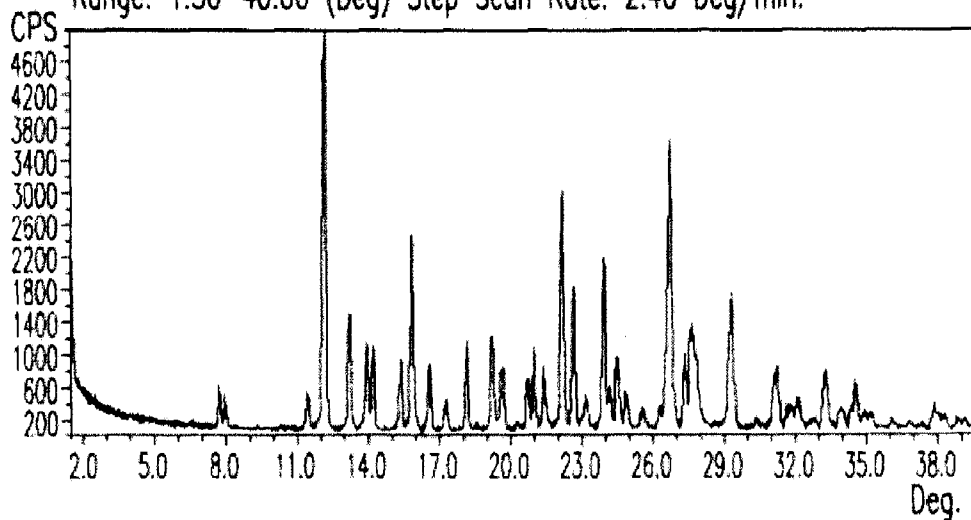


FIG.33

CERTIFICATE OF CORRECTION (continued)

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XRPD PATTERN OF POLYMORPH B

File: Process 5222-157-C

Date: 06/04/04 15:07 Step: 0.020° Cnt Time: 0.500 Sec.

Range: 1.50-40.00 (Deg) Step Scan Rate: 2.40 Deg/min.

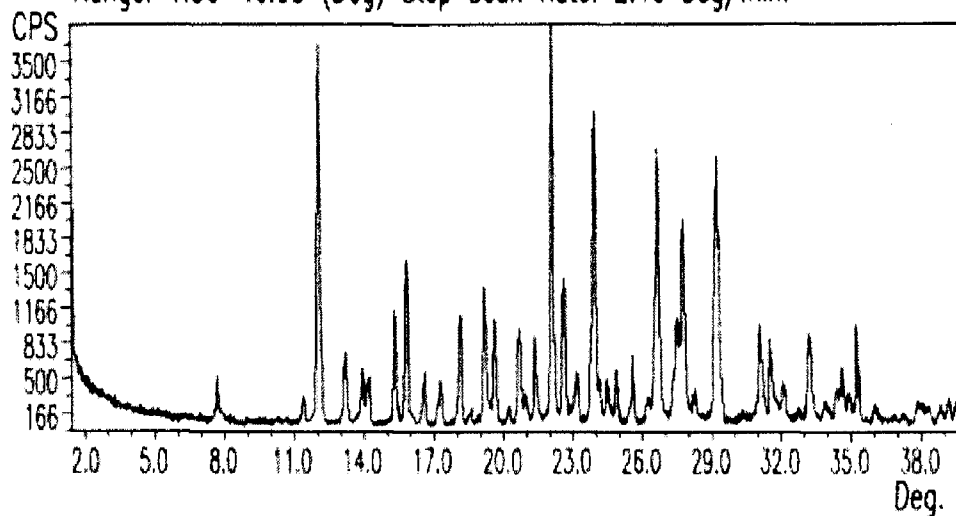


FIG.34

XRPD PATTERN OF POLYMORPH E

File: Process 5222-152-B Form E

Date: 05/21/04 10:46 Step: 0.020° Cnt Time: 0.500 Sec.

Range: 1.50-40.00 (Deg) Step Scan Rate: 2.40 Deg/min.

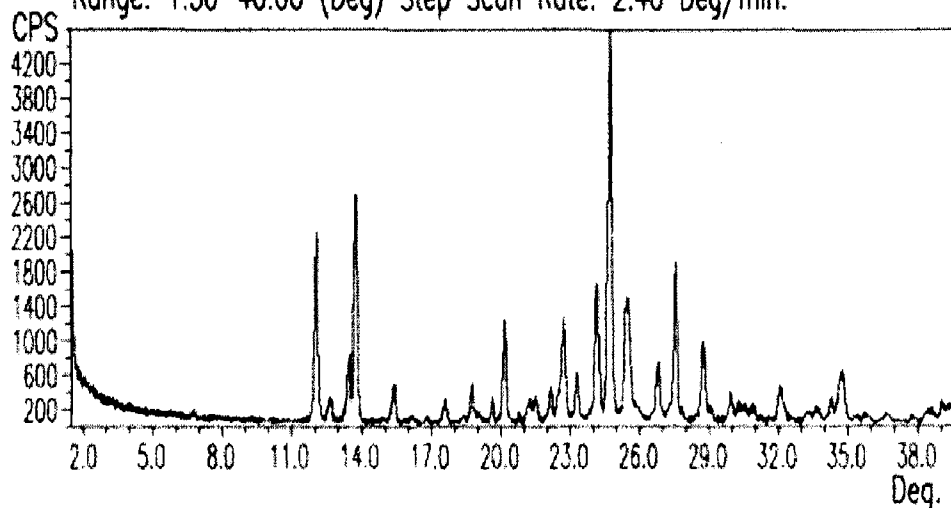


FIG.35

CERTIFICATE OF CORRECTION (continued)

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TGA CURVE OF POLYMORPH B
Sample: 5274-104-B
Size 7.8320mg
Method: Ramp
TGA
Run Date: 09-Jun-04 17:04
Instrument: TGA 0.500 V5.3 Build 171

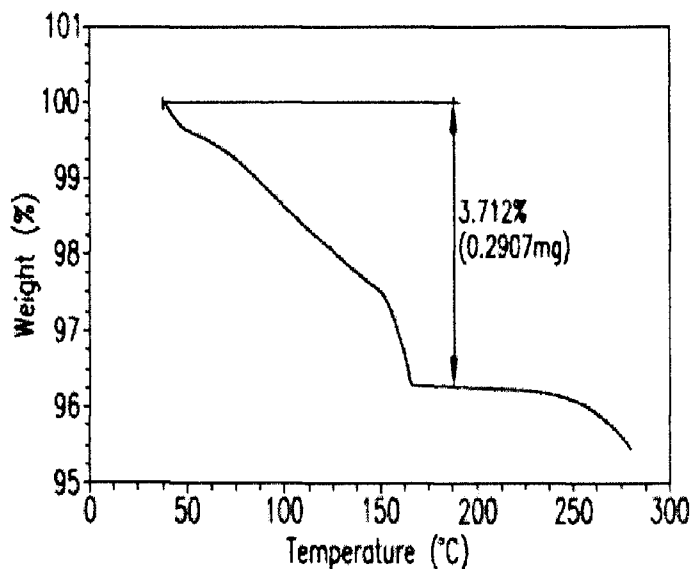


FIG.37

TGA CURVE OF POLYMORPH B
Sample: 5274-100-C
Size 10.9430mg
Method: Ramp
Comment: Evotec Batch 1675C H2O
TGA
Run Date: 03-Jun-04 11:20
Instrument: TGA 0.500 V5.3 Build 171

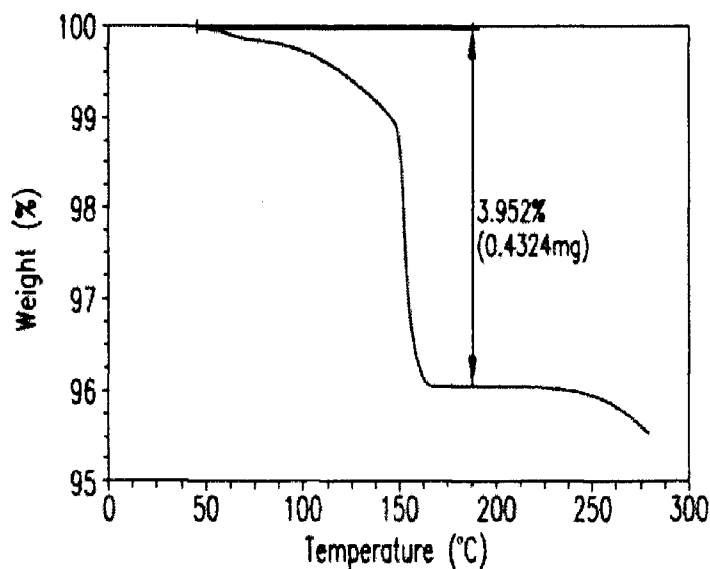


FIG.38

CERTIFICATE OF CORRECTION (continued)

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TGA CURVE OF POLYMORPH B
TGA
Sample: 5222-157-C
Size: 24.4610mg
Method: Ramp
Comment: Evotec Batch 17
Run Date: 07-Jun-04 09:46
Instrument: TGA 0.500 V5.3 Build 171

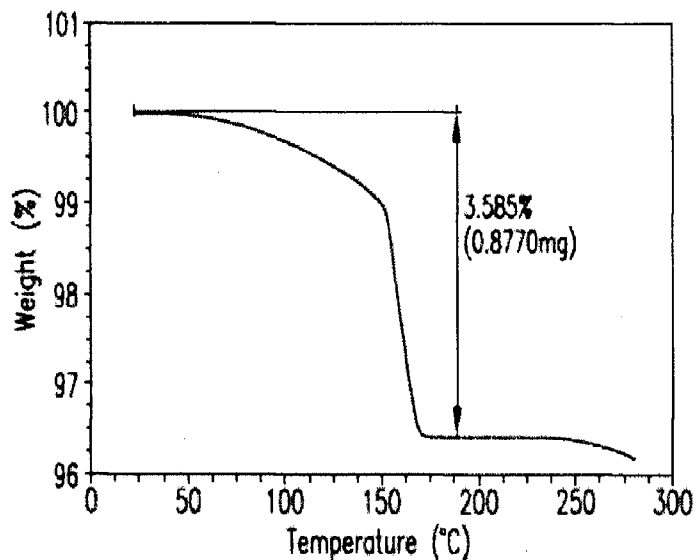


FIG.39

TGA CURVE OF POLYMORPH E
TGA
Sample: 5222-152-B
Size: 11.3850mg
Method: Ramp
Comment: Form E
Run Date: 21-May-04 09:34
Instrument: TGA 0.500 V5.3 Build 171

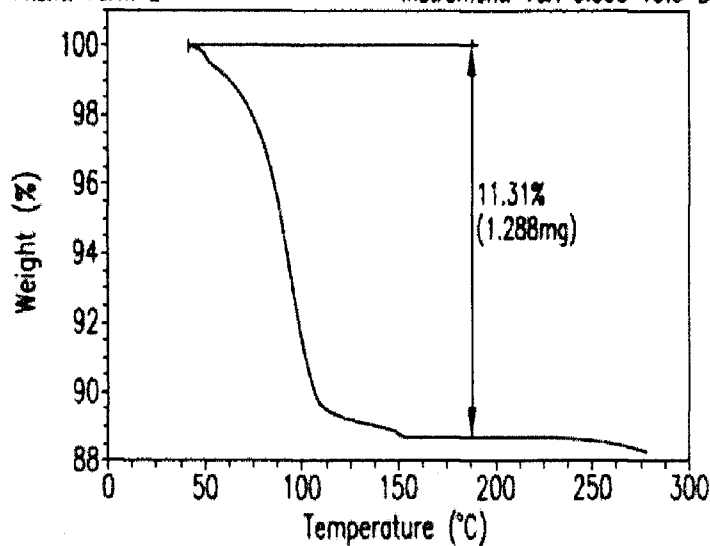


FIG.40

CERTIFICATE OF CORRECTION (continued)

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DSC OF POLYMORPH B
DSC
Sample: 5274-104-B
Size: 0.0000mg
Method: Cell constant calibration
Run Date: 07-Jun-04 11:30
Comment: QAI batch 15 22b
Instrument: DSC Q 1000 V7.3 Build 249

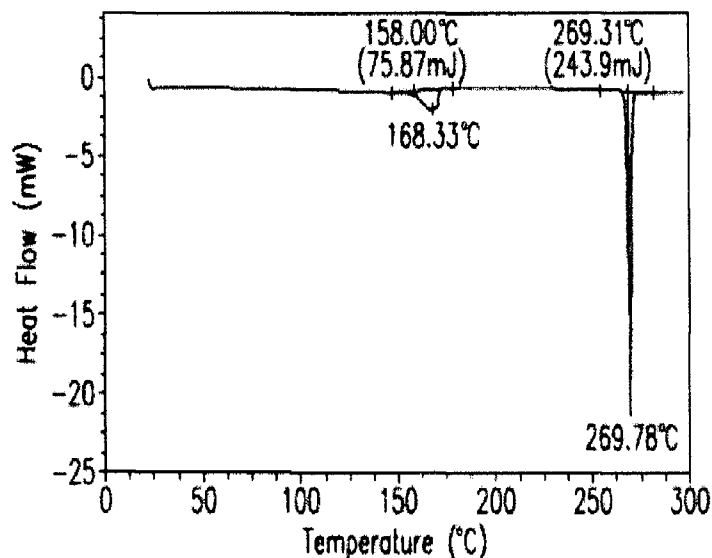


FIG.42

DSC OF POLYMORPH B
DSC
Sample: 5274-100-C
Size: 0.0000mg
Method: Cell constant calibration
Run Date: 02-Jun-04 17:01
Comment: Evotec Batch 1675C 10vol H2O 24h 3h dry
Instrument: DSC Q 1000 V7.3 Build 249

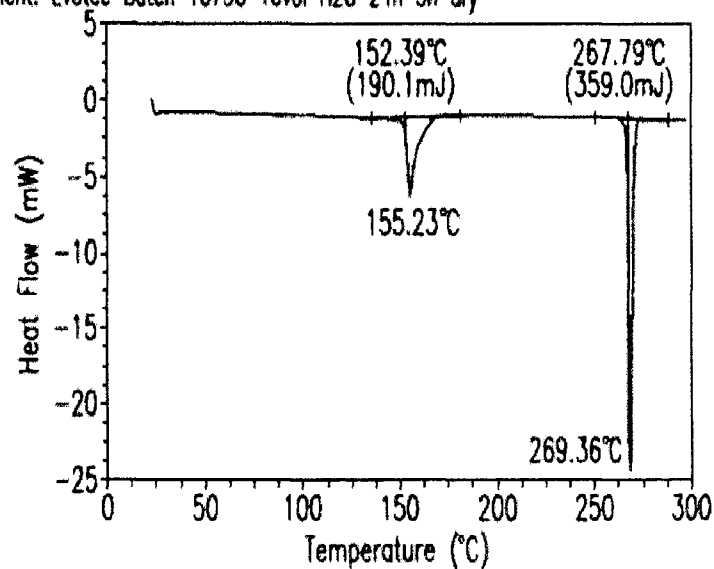


FIG.43

CERTIFICATE OF CORRECTION (continued)

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DSC OF POLYMORPH B
DSC
Sample: 5222-157-C
Size: 0.0000mg
Method: Cell constant calibration
Run Date: 07-Jun-04 09:45
Comment: OAI batch 17
Instrument: DSC Q 1000 V7.3 Build 249

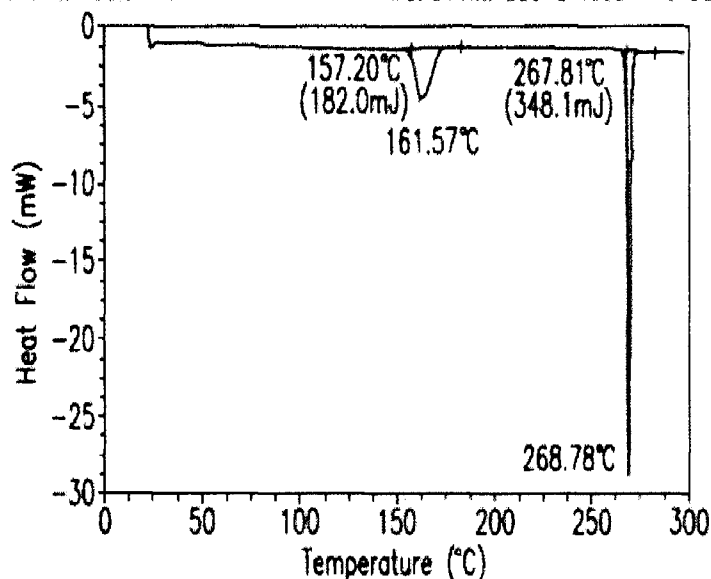


FIG.44

DSC OF POLYMORPH E
DSC
Sample: 5222-152-B
Size: 3.4500mg
Method: Cell constant calibration
Run Date: 21-May-04 09:32
Comment: Evotec batch 15 Form E
Instrument: DSC Q 1000 V7.3 Build 249

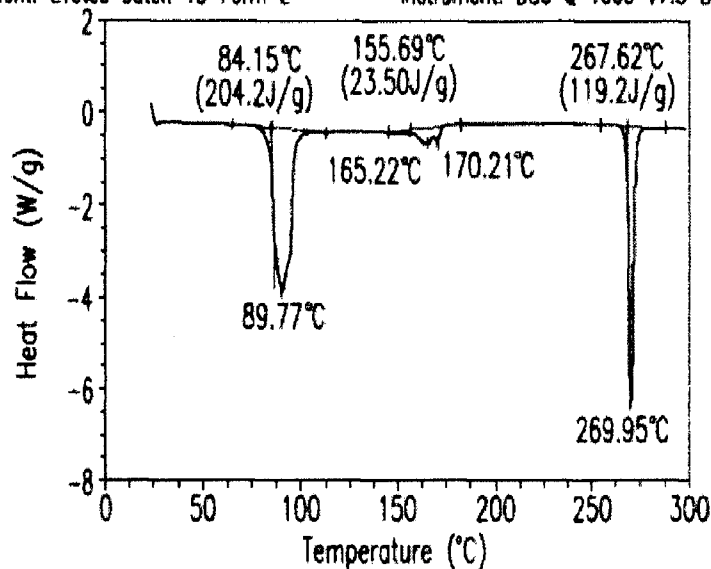


FIG.45

CERTIFICATE OF CORRECTION (continued)

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DSC OF POLYMORPH MIXTURE

Sample: 5222-161-A

DSC

Size: 0.0000mg

Method: Cell constant calibration

Run Date: 11-Jun-04 12:44

Comment: OAI batch 15

Instrument: DSC Q 1000 V7.3 Build 249

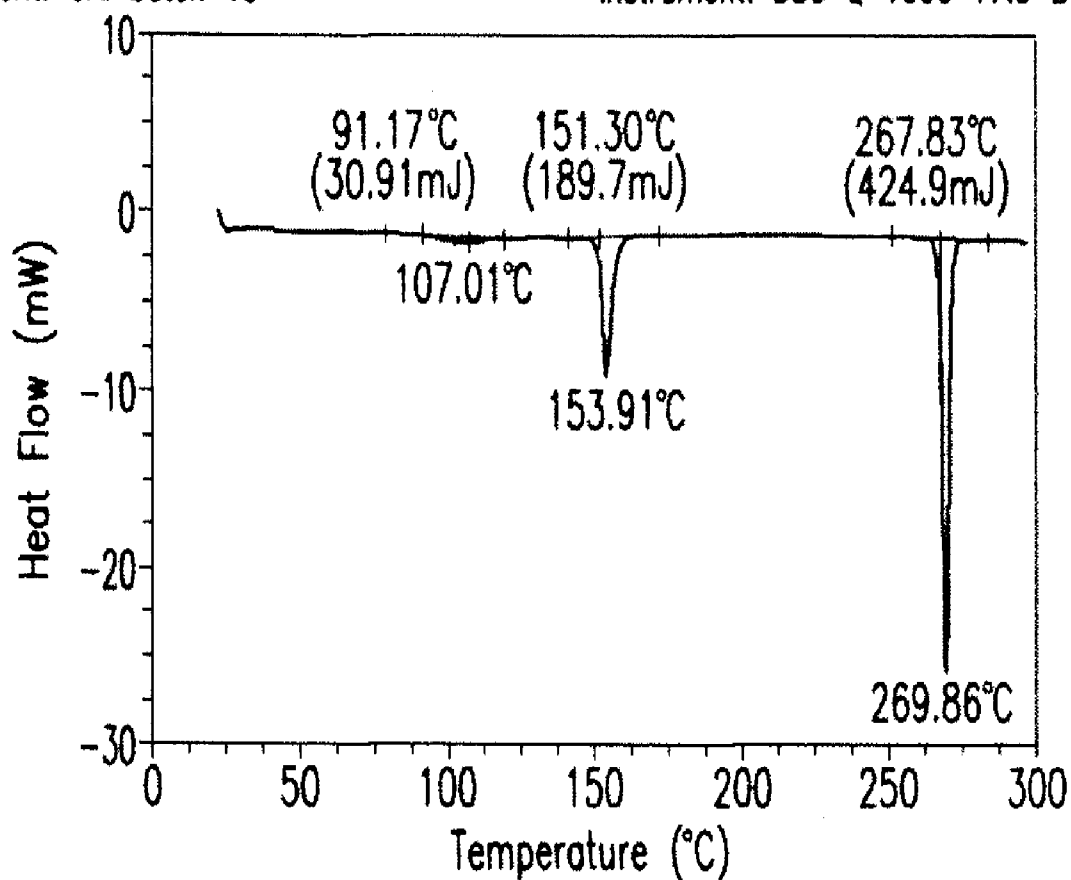


FIG.46

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,465,800 B2
APPLICATION NO. : 10/934863
DATED : December 16, 2008
INVENTOR(S) : Jaworsky et al.

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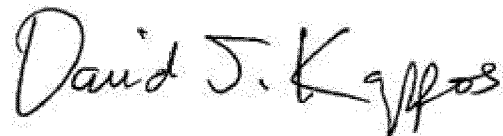
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b)
by 966 days.

Signed and Sealed this
Fifteenth Day of May, 2012

A handwritten signature in black ink that reads "David J. Kappos". The signature is written in a cursive, flowing style.

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT G



US007855217B2

(12) **United States Patent**
Jaworsky et al.(10) **Patent No.:** **US 7,855,217 B2**
(45) **Date of Patent:** ***Dec. 21, 2010**(54) **POLYMORPHIC FORMS OF
3-(4-AMINO-1-OXO-1,3
DIHYDRO-ISOINDOL-2-YL)-
PIPERIDINE-2,6-DIONE**(75) Inventors: **Markian S. Jaworsky**, Hopewell, NJ
(US); **Roger Shen-Chu Chen**, Edison,
NJ (US); **George W. Muller**,
Bridgewater, NJ (US)(73) Assignee: **Celgene Corporation**, Summit, NJ (US)(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 82 days.This patent is subject to a terminal dis-
claimer.(21) Appl. No.: **12/335,395**(22) Filed: **Dec. 15, 2008**(65) **Prior Publication Data**

US 2009/0149500 A1 Jun. 11, 2009

Related U.S. Application Data(62) Division of application No. 10/934,863, filed on Sep.
3, 2004, now Pat. No. 7,465,800.(60) Provisional application No. 60/499,723, filed on Sep.
4, 2003.(51) **Int. Cl.****A61K 31/454** (2006.01)**C07D 401/04** (2006.01)(52) **U.S. Cl.** **514/323**; 546/200(58) **Field of Classification Search** 514/323;
546/200

See application file for complete search history.

(56) **References Cited****U.S. PATENT DOCUMENTS**

3,536,809 A 10/1970 Applezweig
3,598,123 A 8/1971 Zaffaroni
3,845,770 A 11/1974 Theeuwes et al.
3,916,899 A 11/1975 Theeuwes et al.
4,008,719 A 2/1977 Theeuwes et al.
4,810,643 A 3/1989 Souza
4,999,291 A 3/1991 Souza
5,059,595 A 10/1991 Le Grazie
5,073,543 A 12/1991 Marshall et al.
5,120,548 A 6/1992 McClelland et al.
5,229,496 A 7/1993 Deeley et al.
5,354,556 A 10/1994 Sparks et al.
5,385,901 A 1/1995 Kaplan et al.
5,391,485 A 2/1995 Deeley et al.
5,393,870 A 2/1995 Deeley et al.
5,528,823 A 6/1996 Rudy, Jr. et al.
5,580,755 A 12/1996 Souza
5,591,767 A 1/1997 Mohr et al.
5,593,990 A 1/1997 D'Amato
5,629,327 A 5/1997 D'Amato
5,635,517 A 6/1997 Muller et al.

5,639,476 A 6/1997 Oshlack et al.
5,674,533 A 10/1997 Santus et al.
5,698,579 A 12/1997 Muller
5,712,291 A 1/1998 D'Amato
5,731,325 A 3/1998 Andrulis, Jr. et al.
5,733,566 A 3/1998 Lewis
5,798,368 A 8/1998 Muller et al.
5,874,448 A 2/1999 Muller et al.
5,877,200 A 3/1999 Muller
5,929,117 A 7/1999 Muller et al.
5,955,476 A 9/1999 Muller et al.
6,020,358 A 2/2000 Muller et al.
6,071,948 A 6/2000 D'Amato
6,114,335 A 9/2000 D'Amato
6,114,355 A 9/2000 D'Amato
6,140,346 A 10/2000 Andrulis, Jr. et al.
6,235,756 B1 5/2001 D'Amato
6,281,230 B1 8/2001 Muller et al.
6,316,471 B1 11/2001 Muller et al.
6,326,388 B1 12/2001 Man et al.
6,335,349 B1 1/2002 Muller et al.
6,380,239 B1 4/2002 Muller et al.
6,395,754 B1 5/2002 Muller et al.
6,403,613 B1 6/2002 Man et al.
6,420,414 B1 7/2002 D'Amato
6,458,810 B1 10/2002 Muller et al.
6,469,045 B1 10/2002 D'Amato
6,476,052 B1 11/2002 Muller et al.
6,518,298 B2 2/2003 Green et al.
6,555,554 B2 4/2003 Muller et al.

(Continued)

FOREIGN PATENT DOCUMENTS

JP A H10-53576 2/1998

(Continued)

OTHER PUBLICATIONSDimartino et al., 1997, "Preparation and physical characterization of
forms II and III of paracetamol," J. Thermal Analysis 48:447-458.

(Continued)

Primary Examiner—Celia Chang
(74) *Attorney, Agent, or Firm*—Jones Day(57) **ABSTRACT**Polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoin-
dol-2-yl)-piperidine-2,6-dione are disclosed. Compositions
comprising the polymorphic forms, methods of making the
polymorphic forms and methods of their use are also dis-
closed.**10 Claims, 48 Drawing Sheets**

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U.S. PATENT DOCUMENTS

7,112,602	B2	9/2006	D'Amato et al.
7,465,800	B2	12/2008	Jaworsky et al.
2001/0018445	A1	8/2001	Huang et al.
2001/0056114	A1	12/2001	D'Amato
2002/0035090	A1	3/2002	Zeldis et al.
2002/0045643	A1	4/2002	Muller et al.
2002/0052398	A1	5/2002	D'Amato
2002/0054899	A1	5/2002	Zeldis
2002/0061923	A1	5/2002	D'Amato
2002/0128228	A1	9/2002	Hwu
2002/0161023	A1	10/2002	D'Amato
2002/0173658	A1	11/2002	Muller et al.
2002/0183360	A1	12/2002	Muller et al.
2003/0013739	A1	1/2003	Masferrer et al.
2003/0028028	A1	2/2003	Man et al.
2003/0045552	A1	3/2003	Robarge et al.
2003/0069428	A1	4/2003	Muller et al.
2003/0096841	A1	5/2003	Robarge et al.
2003/0139451	A1	7/2003	Shah et al.
2003/0144325	A1	7/2003	Muller et al.
2003/0181428	A1	9/2003	Green et al.
2003/0187024	A1	10/2003	D'Amato
2003/0191098	A1	10/2003	D'Amato
2003/0235909	A1	12/2003	Hariri et al.
2004/0029832	A1	2/2004	Zeldis
2004/0077685	A1	4/2004	Figg et al.
2004/0077686	A1	4/2004	Dannenberg et al.
2004/0087546	A1	5/2004	Zeldis
2004/0091455	A1	5/2004	Zeldis
2004/0122052	A1	6/2004	Muller et al.
2004/0220144	A1	11/2004	Zeldis
2004/0266809	A1	12/2004	Emanuel et al.
2005/0203142	A1	9/2005	Zeldis
2006/0052609	A1	3/2006	Muller et al.
2008/0064876	A1	3/2008	Muller et al.
2008/0132541	A1	6/2008	Zeldis et al.
2009/0062343	A1	3/2009	Jaworsky et al.
2009/0149449	A1	6/2009	Liu et al.
2009/0149499	A1	6/2009	Jaworsky et al.
2009/0176832	A1	7/2009	Jaworsky et al.
2009/0187023	A1	7/2009	Jaworsky et al.

FOREIGN PATENT DOCUMENTS

JP	A 2001-503384	3/2001
WO	WO97/46526 A1	12/1997
WO	WO 98/03502	1/1998
WO	WO98/03502 A1	1/1998
WO	WO 98/54170	12/1998
WO	WO 01/70275	9/2001
WO	WO 01/87307	11/2001
WO	WO 02/059106	8/2002
WO	WO 02/064083	8/2002
WO	PCT/US03/11578	1/2003
WO	WO 03097052	11/2003
WO	WO02/26737 A1	4/2004
WO	WO 2004103274	12/2004
WO	WO 2005023192	3/2005
WO	WO 2006/028964 A1	3/2006
WO	WO 2007/136640 A2	11/2007
WO	WO 2009/111948 A1	9/2009
WO	WO 2009/114601 A2	9/2009
WO	WO 2010/054833	5/2010
WO	WO 2010/056384	5/2010
WO	WO 2010/061209	6/2010

WO WO 2010/100476 9/2010

OTHER PUBLICATIONS

Jonsson, 1972, "Chemical structure and teratogenic properties. 3. A review of available data on structure-activity relationships and mechanism of action of thalidomide analogues," *Acta. Pharm. Suec.* 9(6):521-542.

Wilen et al., 1977, "Strategies in optical resolutions," *Tetrahedron* 33:2725-2736.

Wilen, 1972, *Tables of Resolving Agents and Optical Resolutions*, Eliel, ed., U. Notre Dame Press, Notre Dame, IN pp. 268.

Wolff, ed., 1995, *I Burger's Medicinal Chemistry and Drug Discovery*, 5th ed., pp. 172-178 and 949-982.

Corral et al., 1999, "Immunomodulation by thalidomide and thalidomide analogs," *Ann. Rheum. Dis.* 58(Supp. 1):1107-1113.

Grant, 1999, "Theory and Origin of Polymorphism," in *Polymorphism in Pharmaceutical Solids*, Minneapolis, MN, Ch. 1, pp. 1-10.

He, W., et al., 1993, 206th American Chemical Society, Chicago, IL; *Med. Chem.*, paper 216.

Lentzsch et al., 2002, "S-3-Amino-phthalimido-glutarimide inhibits angiogenesis and growth of B-cell neoplasias in mice," *Cancer Research* 62:2300-2305.

Muller et al., 1999, "Amino-substituted thalidomide analogs: Potent inhibitors of TNF- γ production," *Bioorg. Med. Chem. Lett.* 9:1625-1630.

Muller et al., 1998, "Thalidomide analogs and PDE4 inhibition," *Bioorg. Med. Chem. Lett.* 8:2669-2674.

Muller et al., 1996, "Structural modifications of thalidomide produce analogs with enhanced tumor necrosis factor inhibitory activity," *J. Med. Chem.* 39:3238-3240.

Anderson, "Moving disease biology from the laboratory to the clinic," *Seminars in Oncology*, 2002 29:17-20.

Barlogie et al., "High-dose therapy immunomodulatory drugs in multiple myeloma," *Seminars in Oncology*, 2002, 29 (6):26-33.

Barlogie et al., "Introduction: Thalidomide and the IMiDs in multiple myeloma," *Seminars in Hematology*, 2003, 40 (4):1-2.

Barlogie et al., "Total Therapy II (TTII) for newly diagnosed multiple myeloma (MM): preliminary data on feasibility and efficacy in the first 231 enrolled patients; comparison with predecessor trial total therapy I (TTI) (N=231)," *Blood, Abstract # 2857*, Dec. 7-11, 2001, *American Society of Hematology*.

Barlogie, "Thalidomide and CC-5013 in Multiple Myeloma: The University of Arkansas experience," *Seminars in Hematology*, 2003, 40 (4):33-38.

Bartlett et al., "Phase I study to determine the safety, tolerability and immunostimulatory activity of thalidomide analogue CC-5013 in patients with metastatic malignant melanoma and other advanced cancers," *British Journal of Cancer*, 2004, 90:955-961.

Bartlett et al., "The evolution of thalidomide and its IMiD derivatives as anticancer agents," *Nature Reviews Cancer*, 2004, 4 (4):1-9.

Battegay, "Angiogenesis: mechanistic insights, neovascular diseases, and therapeutic prospects," *J. Mol. Med.*, 1995, 73:333-346.

Baz et al., "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and revlimid (R) (DdVd-R) results in a high response rate in patients with refractory multiple myeloma (RMM)," *Blood, Abstract # 2559*, *American Society of Hematology*, Dec. 10-13, 2005.

Brennen et al., "Thalidomide and analogues: current proposed mechanisms and therapeutic usage," *Clinical Prostate Cancer*, 2004, 3 (1):54-61.

Celgene Corporation, "Additional clinical data presented on Revimid™ in myelodysplastic syndromes at the American Society of Hematology 45th annual meeting," Press Release, Dec. 2003.

Celgene Corporation, "Blood reports Revimid™ has anti-tumor activity in patients with relapsed and refractory multiple myeloma," Press Release, Nov. 1, 2002.

Celgene Corporation, "Celgene advances immunomodulatory drug (IMiD™) clinical program," Press Release, Feb. 2000.

Celgene Corporation, "Celgene announces plans to stop phase III trials in melanoma due to lack of efficacy," Press Release, Apr. 2004.

US 7,855,217 B2

Page 3

- Celgene Corporation, "Celgene corporation advances ACTIMID™ (CC-4047) into phase II trial for prostate cancer," Press Release, Oct. 2003.
- Celgene Corporation, "Celgene Corporation announces fourth quarter and full year results for 2002," Press Release, Jan. 2003.
- Celgene Corporation, "Celgene Corporation announces third quarter results. THALOMID® (thalidomide) revenue increases 41% to \$30.5 million. Pivotal programs for THALOMID and REVIMID™ finalized. Peer-reviewed publications of THALOMID and REVIMID data. First JNK inhibitor advanced to Phase I clinical trial," Press Release, Oct. 2002.
- Celgene Corporation, "Celgene Corporation announces third quarter results. Thalomid® (thalidomide) sales increase 24%. Prescriptions up 50%. Enhanced S.T.E.P.S.® launched. Pilot d-MPH data presented," Press Release, Oct. 2001.
- Celgene Corporation, "Celgene Corporation receives orphan drug designation for Revimid™ for multiple myeloma," Press Release, Oct. 2001.
- Celgene Corporation, "Celgene corporation reports record operating performance in first quarter with strong revenue growth and profits," Press Release, Apr. 2004.
- Celgene Corporation, "Celgene corporation reports record operating performance in third quarter as total revenue increases 117% and profits rise," Press Release, Oct. 2003.
- Celgene Corporation, "Celgene corporation reports strong operating performance in second quarter as total sales increase 100 percent and profits rise," Press Release, Jul. 2003.
- Celgene Corporation, "Celgene corporation reviews 2003 achievements and announces 2004 financial outlook," Press Release, Jan. 2004.
- Celgene Corporation, "Celgene expands clinical development program for Revimid™. Five additional trials of Revimid initiated in hematological and solid tumor cancers," Press Release, Jun. 2002.
- Celgene Corporation, "Celgene provides update on clinical pipeline. Celgene Announces first target indication for ACTIMID™, CC-8490. SelCID™ program to advance based on results from Phase I/II trial of CC-1088. First JNK inhibitor successfully completes phase I trial," Press Release, Jan. 2003.
- Celgene Corporation, "Celgene receives fast track status from FDA for Revimid™ in multiple myeloma," Press Release, Feb. 2003.
- Celgene Corporation, "Celgene receives fast track status from FDA for Revimid™ in myelodysplastic syndromes," Press Release, Apr. 2003.
- Celgene Corporation, "Initial Phase I solid tumor data on Celgene's lead IMiD™, Revimid™," Press Release, Jun. 2001.
- Celgene Corporation, "New Revimid™ clinical data shows potential as novel approach to treating myelodysplastic syndromes (MDS)," Press Release, May 2003.
- Celgene Corporation, "Revlimid™ receives orphan drug designation from the European commission for multiple myeloma," Press Release, Feb. 2004.
- Celgene Corporation, "Revlimid™ receives orphan drug designation from the European commission for myelodysplastic syndromes," Press Release, Mar. 2004.
- Chaundhry, 1966, *Cancer Research*, "Effect of Prednisolone and Thalidomide on Induced Submandibular Gland Tumors in Hamster," 26(part 1):1884-86.
- Corral et al., 1999, "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha," *J. Immunol.* 163(1):380-386.
- Craig et al., 1967, "Potential anticancer agents. III. 2-phthalimidoaldehydes and derivatives," *Potential Anticancer Agents* III 10:1071-1073.
- D'Amato et al., 2001, "Mechanism of action of thalidomide and 3-aminothalidomide in multiple myeloma," *Semin. Oncol.* 28:597-601.
- Dalgleish et al., "Thalidomide analogues CC-5013 and CC-4047 induce T cell activation and IL-12 production in patients with both solid tumours and relapsed and refractory multiple myeloma," *British Journal of Cancer*, 2003, 88(Suppl I). S25-S54.
- Dalgleish, et al., "New thalidomide analogues; anti-cancer, anti-angiogenic and immunostimulatory," *British Journal of Cancer*, 2001, 85 (1)25.
- Davies et al., "Thalidomide (Thal) and immunomodulatory derivatives (IMiDs) augment natural killer (NK) cell cytotoxicity in multiple myeloma ~MM)," Abstract # P222, *VIIIth International Myeloma Workshop*, May 4-8, 2001.
- Davies et al., "Thalidomide (Thal) and immunomodulatory derivatives (IMiDs) augment natural killer (NK) cell cytotoxicity in multiple myeloma(MM)," Abstract # 3617, *American Society of Hematology*, Dec. 1-5, 2000.
- Davies et al., 2001, "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma," *Blood* 98(1):210-216.
- Dibbs et al., "Thalidomide and thalidomide analogs suppress TNF α secretion by myocytes," Abstract # 1284, *Circulation*, 1998.
- Dimopoulos et al., "Results of thalidomide and IMiDs in multiple myeloma," Abstract # P12.1.4, *International Multiple Myeloma Workshop*, May 23-27, 2003.
- Dimopoulos et al., "Study of lenalidomide plus dexamethasone versus dexamethasone alone in relapsed or refractory multiple myeloma (MM): Results of a phase 3 Study (MM-010)," Abstract # 6, *American Society of Hematology*, Dec. 10-13, 2005.
- Dimopoulos et al., "Treatment of plasma cell dyscrasias with thalidomide and its derivatives," *Journal of Clinical Oncology*, Dec. 1, 2003, 21 (23):4444-4454.
- Dimopoulos et al., 2004, "Primary treatment with pulsed melphalan, dexamethasone, thalidomide (MDT) for symptomatic patients with multiple myeloma ≤ 75 years of age," *Am. Soc. Hematol.* 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract # 1482.
- Dredge et al., "A costimulatory thalidomide analog enhances the partial anti-tumor immunity of an autologous vaccination in a model of colorectal cancer," Abstract # 491, *American Association for Cancer Research*, Apr. 6-10, 2002.
- Dredge et al., "Adjuvants and the promotion of Th1-type cytokines in tumour immunotherapy," *Cancer Immunol Immunother.*, 2002, 51:521-531.
- Dredge et al., "Angiogenesis inhibitors in cancer therapy," *Current Opinion in Investigational Drugs*, 2003, 4 (6):667-674.
- Dredge et al., "Immunological effects of thalidomide and its chemical and functional analogs," *Critical Reviews in Immunology*, 2002, 22 (5&6):425-437.
- Dredge et al., "Protective antitumor immunity induced by a costimulatory thalidomide analog in conjunction with whole tumor cell vaccination is mediated by increased Th1-type immunity¹," *The Journal of Immunology*, 2002, 168:4914-4919.
- Dredge et al., "Recent developments in antiangiogenic therapy," *Expert Opin. Biol. Ther.*, 2002, 2 (8):953-966.
- Dredge et al., "Thalidomide analogs as emerging anti-cancer drugs," *Anti-Cancer Drugs*, 2003, 14:331-335.
- Dredge et al., 2002, "Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects," *Br. J. Cancer* 87(10):1166-1172.
- Fickentscher et al., "Stereochemical properties and teratogenic activity of some tetrahydrophthalimides," *Molecular Pharmacology*, 1976, 13:133-141.
- Galustian et al., "Thalidomide-derived immunomodulatory drugs as therapeutic agents," *Expert Opin. Biol. Ther.*, 2004, 4 (12):1-8.
- Glaspay et al., "The potential role of thalidomide and thalidomide analogs in melanoma," *Clinical Advances in Hematology & Oncology*, 2004, 1-7.
- Gupta et al., "Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications," *Leukemia*, 2001, 15:1950-1961.
- Haslett et al., 2003, "Thalidomide and a thalidomide analogue drug costimulate virus-specific CD8 + T cells in vitro," *J. Infect. Dis.* 187(6):946-955.
- Hayashi et al., "Mechanisms whereby immunomodulatory analogs of thalidomide augment autologous NK cell anti-myeloma immunity," *Blood*, Abstract # 3219, Dec. 6-10, 2002, *American Society of Hematology*.
- He, W., et al., 1993, Abstract of papers. 206th American Chemical Society, Chicago, IL; Med. Chem., paper 216.
- Helm et al., "Comparative teratological investigation of compounds of structurally arid pharmacologically related to thalidomide," *Arzneimittel Forschung Drug Research*, 1981, 31 (1)941-949.

US 7,855,217 B2

Page 4

- Hernandez-Illizaliturri et al., "Addition of immunomodulatory drugs CC5013 or CC4047 to rituximab enhances anti-tumor activity in a severe combined immunodeficiency (SCID) mouse lymphoma model," *Abstract # 235, American Society of Hematology*, Dec. 6-9, 2003.
- Hideshima et al., "Thalidomide (Thal) and its analogs overcome drug resistance of human multiple myeloma (MM) cells to conventional therapy," *Abstract 1313, American Society of Hematology*, Dec. 1-5, 2000.
- Hideshima et al., "Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy," *Blood*, 2000, 96:2943-2950, *American Society of Hematology*.
- Hunt et al., "Markers of endothelial and haemostatic activation in the use of CC-4047, a structural analogue of thalidomide, in relapsed myeloma," *Blood, Abstract # 3216*, Dec. 6-10, 2002, *American Society of Hematology*.
- Hussein et al., "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and Revlimid (DVD-R) a phase I/II trial in advanced relapsed/refractory multiple myeloma (Rmm) patients," *Blood, Abstract #208, American Society of Hematology*, Dec. 4-7, 2004.
- Kyle et al., "Multiple myeloma," *New England Journal of Medicine*, 2004, 351:1860-1873.
- Kyle, "Current therapy of multiple myeloma," *Internal Medicine*, 2002, 41 (3):175-180.
- Leblanc et al., "Immunomodulatory drug costimulates T cells via the B7-CD28 pathway," *Blood*, 2004, 103:1787-1790, *American Society of Hematology*.
- Lentzsch et al., "Immunomodulatory derivative of thalidomide (IMiD CC-4047) determine the lineage commitment of hematopoietic progenitors by down regulation of GATA-1 and modulation of cytokine secretion," *Abstract # 3073, American Society of Hematology*, Dec. 6-9, 2003.
- Lentzsch et al., "Immunomodulatory derivative of thalidomide (IMiD CC-4047) down regulates CAAT/enhancer-binding protein β (C/EBP β) in multiple myeloma (MM)," *Abstract # 3456, American Society of Hematology*, Dec. 6-9, 2003.
- Lentzsch et al., "In vivo activity of thalidomide and immunomodulatory drugs against multiple myeloma," *VIIIth International Myeloma Workshop, Abstract #P225*, May 4-8, 2001.
- Lentzsch et al., 2003, "Immunomodulatory analogs of thalidomide inhibit growth of Hs Sultan cells and angiogenesis in vivo," *Leukemia* 17(1):41-44.
- Liu et al., "Phase I study of CC-5013 (Revimid), a thalidomide derivative, in patients with refractory metastatic cancer," *American Society of Oncology, Abstract #927*, 2003.
- Luzzio et al., "Thalidomide analogues: derivatives of an orphan drug with diverse biological activity," *Expert Opin. Ther. Patents*, 2004, 14 (2):215-229.
- Man et al., " α -Fluoro-substituted thalidomide analogues," *Bioorganic & Medicinal Chemistry Letters* 13, 2003, 3415-3417.
- Marriott et al., "A novel subclass of thalidomide analogue with anti-solid tumor activity in which caspase-dependent apoptosis is associated with altered expression of bcl-2 family proteins," *Cancer Research*, 2003, 63:593-599.
- Marriott et al., "Immunotherapeutic and antitumor potential of thalidomide analogues," *Expert Opin. Biol. Ther.*, 2001, 1 (4):1-8.
- Marriott et al., "New thalidomide analogues; anti-cancer, anti-angiogenic and immunostimulatory," *British Journal of Cancer*, 85:25, Jul. 6, 2001.
- Marriott et al., "Thalidomide and its analogues have distinct and opposing effects on TNF- α and TNFR2 during co-stimulation of both CD4⁺ and CD8⁺ T cells," *Clin. Exp. Immunol.*, 2002, 130:75-84.
- Marriott et al., "Thalidomide derived immunomodulatory drugs (IMiDs) as potential therapeutic agents," *Current Drug Targets—Immune, Endocrine & Metabolic Disorders*, 2003, 3:181-186.
- Masellis et al., "Changes in gene expression in bone marrow mesenchymal progenitor cells as a consequence of IMiD therapy in multiple myeloma patients," *Blood, Abstract # 1548*, Dec. 7-11, 2001, *American Society of Hematology*.
- McCarty, "Thalidomide may impede cell migration in primates by down-regulating integrin β -chains: potential therapeutic utility in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis," *Medical Hypotheses*, 1997, 49:123-131.
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs (Imids) in human multiple myeloma cells: therapeutic implications," *Abstract # 3224*, Dec. 7-11, 2001, *American Society of Hematology*.
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications," *Blood*, 2002, 99:4525-4530, *American Society of Hematology*.
- Mitsiades et al., "CC-5013 Celgene," *Current Opinion in Investigational Drugs*, 2004, 5 (6):635-647.
- Miyachi et al., 1997, "Novel biological response modifiers: phthalimides with tumor necrosis factor- α production-regulating activity," *J. Med. Chem.* 40:2858-2865.
- Moutouh et al., "Novel immunomodulatory drugs (IMiDs®): A potential, new therapy for β -hemoglobinopathies," *Abstract # 3740, American Society of Hematology*, Dec. 4-7, 2004.
- Patten et al., "The early use of the serum free light chain assay in patients with relapsed refractory myeloma receiving treatment with a thalidomide analogue (CC-4047)," *Abstract # 1640, American Society of Hematology*, Dec. 6-9, 2003.
- Payvandi et al., "CC-5013 inhibits the expression of adhesion molecules ICAM-1 and CD44 and prevents metastasis of B16 F10 mouse melanoma cells in an animal model," *American Society of Clinical Oncology, Abstract # 992*, 2003.
- Payvandi et al., "Effects of a thalidomide analog on binding activity of transcription factors and cell cycle progression of multiple myeloma cell lines," *Blood, Abstract #2487*, Dec. 1-5, 2000, *American Society of Hematology*.
- Payvandi et al., "Immunomodulatory drugs inhibit expression of cyclooxygenase-2 from TNF- α , IL-1 β , and LPS-stimulated human PBMC in a partially IL-10-dependent manner," *Cellular Immunology*, 2004, 81-88.
- Payvandi et al., "Thalidomide and IMiDs inhibit microvessel formation from human arterial rings in the absence of human liver microsomes," *Blood, Abstract # 5046*, Dec. 6-10, 2002, *American Society of Hematology*.
- Payvandi et al., "Thalidomide analogs IMiDs inhibit expression of cyclooxygenase-2 in multiple myeloma cell line and LPS stimulated PBMCs," *Blood, Abstract # 2689*, Dec. 7-11, 2001, *American Society of Hematology*.
- Payvandi Yvandi et al., "The thalidomide analogs IMiDs enhance expression of CD69 stimulatory receptor on natural killer cells," *Abstract # 1793, American Association for Cancer Research*, Mar. 24-28, 2001.
- Raje et al., "Combination of the mTOR inhibitor rapamycin and CC-5013 has synergistic activity in multiple myeloma," *Blood*, Dec. 15, 2004, 104 (13):4188-4193.
- Rajkumar et al., "Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma," *Blood*, Dec. 15, 2005, 106 (13):4050-4053.
- Richardson et al., "A multi-center, randomized, phase 2 study to evaluate the efficacy and safety of 2 CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM)," *Blood, Abstract # 825, American Society of Hematology*, Dec. 6-9, 2003.
- Richardson et al., "A multicenter, single-arm, open-label study to evaluate the efficacy and safety of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma; preliminary results," *10th International Myeloma Workshop*, Apr. 10-14, 2005.
- Richardson et al., "A Phase I study of oral CC5013, an immunomodulatory thalidomide (Thal) derivative, in patients with relapsed and refractory multiple myeloma (MM)," *Blood, Abstract #3225*, Dec. 7-11, 2001, *American Society of Hematology*.
- Richardson et al., "A phase 1 trial of lenalidomide (REVLIMID®) with bortezomib (VELCADE®) in relapsed and refractory multiple myeloma," *Blood, Abstract # 365, American Society of Hematology*, Dec. 10-13, 2005.
- Richardson et al., "Immunomodulatory analogs of thalidomide: an emerging new therapy in myeloma," *Journal of Clinical Oncology*, 2004, 22(16) 3212-3214.

US 7,855,217 B2

Page 5

- Richardson et al., "Immunomodulatory drug CC-55013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma," *Blood*, 2002 100:3063-3067, *American Society of Hematology*.
- Richardson et al., "Novel biological therapies for the treatment of multiple myeloma," *Best Practice & Research Clinical Haematology*, 2005, 18 (4):619-634.
- Rubin et al., "Principles of cancer treatment-I," 2003, 12 ONCO IV 1.
- Schafer et al., "Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs," *Journal of Pharmacology and Experimental Therapeutics*, 2003, 305(3):1222-1232.
- Schey et al., "A phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma," *Journal of Clinical Oncology*, 2004, 22 (16):1-8.
- Schey et al., "A phase I study of an immunomodulatory thalidomide analogue (CC4047) in relapse/refractory multiple myeloma," *International Society for Experimental Hematology, Abstract #248*, 2002.
- Shah et al., 1999, "Synthesis and enantiomeric separation of 2-phthalimidino-glutaric acid analogues: potent inhibitors of tumor metastasis," *J. Med. Chem.* 42:3014-3017.
- Shaughnessy et al., "Global gene expression analysis shows loss of C-MYC and IL-6 receptor gene mRNA after exposure of myeloma to thalidomide and ImiD," *Abstract # 2485, The American Society of Hematology*, Dec. 1-5, 2000.
- Shire et al., "TNF- α inhibitors and rheumatoid arthritis," *Exp. Opin. Ther. Patents*, 1998, 8 (5):531-544.
- Sorbera et al., "CC-5013. Treatment of multiple myeloma. Treatment of Melanoma. Treatment of myelodysplastic syndrome. Angiogenesis inhibitor. TNF- α production inhibitor," *Drugs of the Future*, 2003, 28(5):425-431.
- Streetly et al., "An update of the use and outcomes of the new immunomodulatory agent CC-4047 (Actimid) in patients with relapsed/refractory myeloma," *Abstract #829, American Society of Hematology*, Dec. 6-9, 2003.
- Streetly et al., "Changes in neutrophil phenotype following the administration of CC-4047 (Actimid) to patients with multiple myeloma," *Abstract # 2543, American Society of Hematology*, Dec. 6-9, 2003.
- Streetly et al., "Thalidomide analogue CC-4047 is effective in the treatment of patients with relapsed and refractory multiple myeloma (MM) and induces T-cell activation and IL-12 production," *Abstract # 367, International Multiple Myeloma Workshop*, May 23-27, 2003.
- Teo et al., "A phase I, single-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacokinetic study of CDC-501, a novel immunomodulatory- oncologic agent, in healthy male subjects with a comparison of fed and fasted," *Clinical Pharmacology and Therapeutics*, 2002, 71 (2):93.
- Teo et al., "Chiral inversion of the second generation ImiD™ CC-4047 (ACTIMID™) in human plasma and phosphate-buffered saline," *Chirality*, 2003, 15:348-351.
- Thertulien et al., "Hybrid MEL/DT PACE autotransplant regimen for Multiple Myeloma (MM)- safety and efficacy data in pilot study of 15 patients," *Blood, Abstract # 2869, American Society of Hematology*, Dec. 7-11, 2001.
- Tohny et al., "A phase I study of oral CC-5013 (lenalidomide, Revlimid™), a thalidomide derivative, in patients with refractory metastatic cancer," *Clinical Prostate Cancer*, 2004, 2:241-243.
- Tricot et al., "Angiochemotherapy (ACT) for multiple myeloma (MM) with DT-PACE results in a high response rate, but in contrast to tandem transplants with melphalan does not affect durable disease control," *Blood, Abstract # 3531, American Society of Hematology*, Dec. 7-11, 2001.
- Tsenova et al., "Use of ImiD3, a thalidomide analog, as an adjunct to therapy for experimental tuberculous meningitis," *Antimicrobial Agents and Chemotherapy*, 2002, 46 (6):1887-1895.
- Weber et al., "A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma," *Abstract # PO.738, International Multiple Myeloma Workshop*, Apr. 10-14, 2005.
- Weber, "Lenalidomide (CC-5013, Revlimid™) and other ImiDs," *Abstract # PL.5.02, International Multiple Myeloma Workshop*, Apr. 10-14, 2005.
- Ye et al., "Novel ImiD drugs enhance expansion and regulate differentiation of human cord blood CD34+ cells with cytokines," *Blood, Abstract #4099, American Society of Hematology*, Dec. 6-10, 2002.
- Zangari et al., "Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDCT)," *American Society of Hematology, Abstract # 3226*, 2001.
- Zangari et al., "Revimid 25 mg (Rev 25) \times 20 versus 50 mg (REV 50) \times 10 q 28 days with bridging of 5 mg \times 10 versus 10 mg \times 5 as post-transplant salvage therapy for multiple myeloma (MM)," *Blood, Abstract # 1642, American Society of Hematology*, Dec. 6-9, 2003.
- Zangari et al., "Risk factors for deep vein thrombosis (DVT) in a large group of myeloma patients (PTS) treated with thalidomide (Thal): The Arkansas Experience," *Blood, Abstract # 681, American Society of Hematology*, Dec. 7-11, 2001.
- Zeldis et al., "Potential new therapeutics for Waldenstrom's macroglobulinemia," *Seminars in Oncology*, 2003, 30 (2):275-281.
- Zeldis et al., "Update on the evolution of the ImiD™," *International Society for Biological Therapy of Cancer. Oral Abstract*, 2003.
- Zhang et al., "CC-5079, a novel microtubule and TNF- α inhibitor with anti-angiogenic and antimetastasis activity," *Abstract # B012, International Conference on Molecular Targets and Cancer Therapeutics*, Nov. 17-21, 2003.
- Haleblian, J.; McCrone, W.; "Pharmaceutical Applications of Polymorphism", *Journal of Pharmaceutical Sciences*, Aug. 1969, 58(8):911-929.
- Davies, F.E.; et al., "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma," *Blood*, Jul. 2001, 98(1):210-216.
- Kyle, R.A.; Rajkumar, S.V., "Therapeutic Application of Thalidomide in Multiple Myeloma," *Seminars in Oncology*, Dec. 2001, 28(6):583-587.
- USPTO Office Action dated Dec. 31, 2007 in currently pending U.S. Appl. No. 10/438,213.
- Office Action dated Apr. 16, 2010 in corresponding Japanese Patent Application No. 2006-525471 (with summary).
- USPTO Office Action dated Oct. 10, 2007 in U.S. Appl. No. 7,465,800.
- Bernstein, 2002, *Polymorphism in Molecular Crystals*, Clarendon Press, 115-18.
- Bernstein, 2004, "Crystal Structure Prediction and Polymorphism," *ACA Transactions*, 39, 14-23.
- Bond et al., 2002, "Controlling Crystal Architecture in Molecular Solids: the Supramolecular Approach," in *Supramolecular Organization and Materials Design*, Jones & Rao eds., Cambridge University Press, Chapter 12, pp. 391-443.
- Brittain, 1999, "Methods for the Characterization of Polymorphs and Solvates," in *Polymorphism in Pharmaceutical Solids*, Brittain ed., Chapter 6, pp. 227-278.
- Brittain, 2002, "Polymorphism: Pharmaceutical Aspects," in *Encyclopedia of Pharmaceutical Technology*, 2nd Edition, vol. 3, Swarbrick & Boylan eds., pp. 2239-2249.
- U.S. Appl. No. 60/499,723, filed Sep. 4, 2003, Jaworsky.
- U.S. Appl. No. 60/372,348, filed Apr. 12, 2002, Hariiri et al.
- U.S. Appl. No. 09/545,654, filed Apr. 10, 2000, D'Amato.
- U.S. Appl. No. 09/287,377, filed Apr. 7, 1999, D'Amato.
- Brittain, 2007, "Polymorphism and Solvatomorphism 2005," *Journal of Pharmaceutical Sciences*, 96(4), 705-28.
- Bruns et al., 1984, "Thermochemical Investigation of Theophylline, Theophylline Hydrate and Their Aqueous Solutions," *Thermochimica Acta*, 72, 31-40.
- Byrn et al., 1999, "Drugs as Molecular Solids," in *Solid-State Chemistry of Drugs*, 2nd Edition, Chapter 1, pp. 3-43.
- Cruz Cabeza et al., 2006, "Prediction and Observation of Isostructurality Induced by Solvent Incorporation in Multicomponent Crystals," *J. Am. Chem. Soc.*, 128, 14466-67.
- Cruz Cabeza et al., 2007, "Importance of Molecular Shape for the Overall Stability of Hydrogen Bond Motifs in the Crystal Structures of Various Carbamazepine-Type Drug Molecules," *Crystal Growth & Design*, 7(1), 100-07.

US 7,855,217 B2

Page 6

- Day et al., 2004, "An Assessment of Lattice Energy Minimization for the Prediction of Molecular Organic Crystal Structures," *Crystal Growth & Design*, 4(6), 1327-40.
- Day et al., 2006, "Investigating the Latent Polymorphism of Maleic Acid," *Chemical Communications*, 54-56.
- Dean, 1993, *Analytical Chemistry Handbook*, 10.24-10.26.
- Gadamasetti et al., 2007, "Process Chemistry in the Pharmaceutical Industry," in *Encyclopedia of Pharmaceutical Technology*, 3rd Edition, vol. 5, Swarbrick ed., pp. 2993-3007.
- Jones et al., 2006, "Pharmaceutical Cocrystals: An Emerging Approach to Physical Property Enhancement," *MRS Bulletin*, 31, 875-79.
- Kirk-Othmer, 2002, "Crystallization," in *Encyclopedia of Chemical Technology*, vol. 8, pp. 95-147.
- Knapman, 2000, "Polymorphic Predictions," *Modern Drug Discovery*, 3(2), 53-57.
- Office Action dated Jun. 18, 2010 in U.S. Appl. No. 12/220,336.
- Richardson et al., "A Multi-Center, Randomized, Phase II Study To Evaluate the Efficacy and Safety of Two CDC-5013 Dose Regimens When Used Alone or in Combination with Dexamethasone (Dex) for the Treatment of Relapsed or Refractory Multiple Myeloma (MM)," *Blood*, Journal of the American Society of Hematology, Dec. 6-10, 2002, 100(11):Abstract #386.
- Seddon, 2004, "Pseudopolymorph: A Polemic," *Crystal Growth & Design*, 4(6), 1087.
- Sharma et al., 2006, "Toxicity Profile of the Immunomodulatory Thalidomide Analogue, Lenalidomide: Phase I Clinical Trial of Three Dosing Schedules in Patients with Solid Malignancies," *European Journal of Cancer*, 42, 2318-25.
- Vippagunta et al., 2001, "Crystalline Solids," *Advanced Drug Delivery Reviews*, 48, 3-26.
- Caira, 1998, "Crystalline Polymorphism of Organic Compounds," *Topics in Current Chemistry*, 198, 163-208.
- Fauci et al, 1998, "Harrison's Principles of Internal Medicine, Chronic Visual Loss," in *Harrison's Principles of Internal Medicine*, 168.
- Notice of Allowability mailed Nov. 3, 2008 in U.S. Appl. No. 10/934,863.
- Office Action mailed Jun. 17, 2010 in U.S. Appl. No. 10/557,302.

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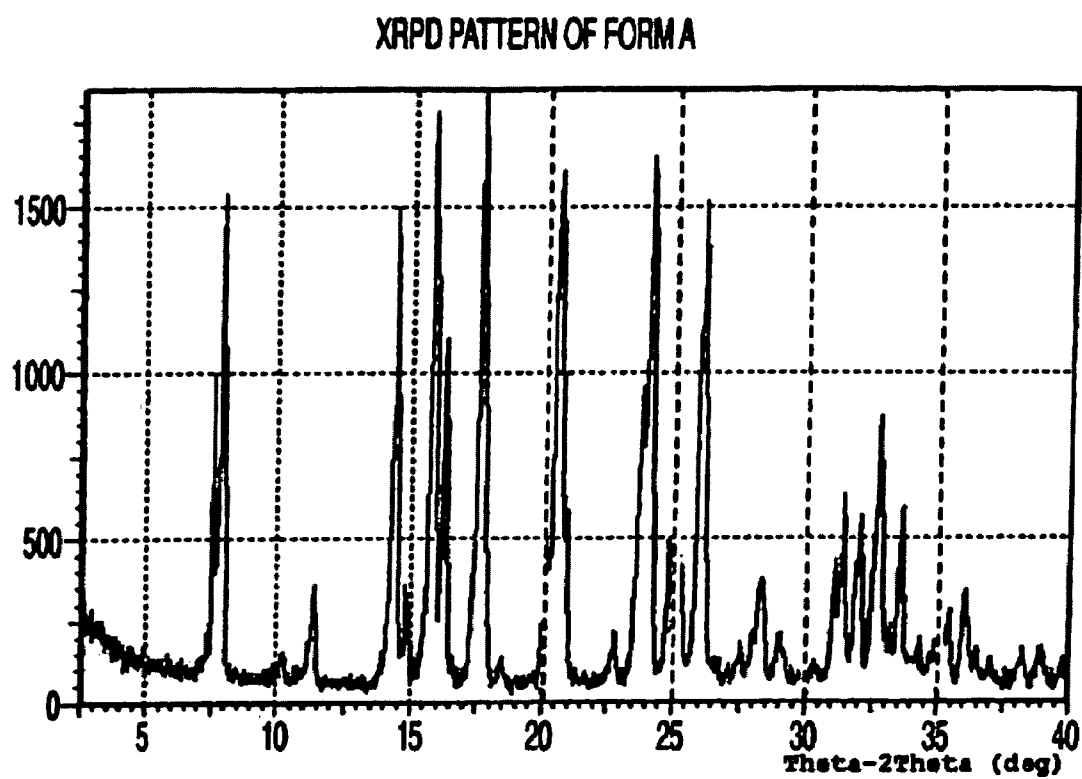


Fig. 1

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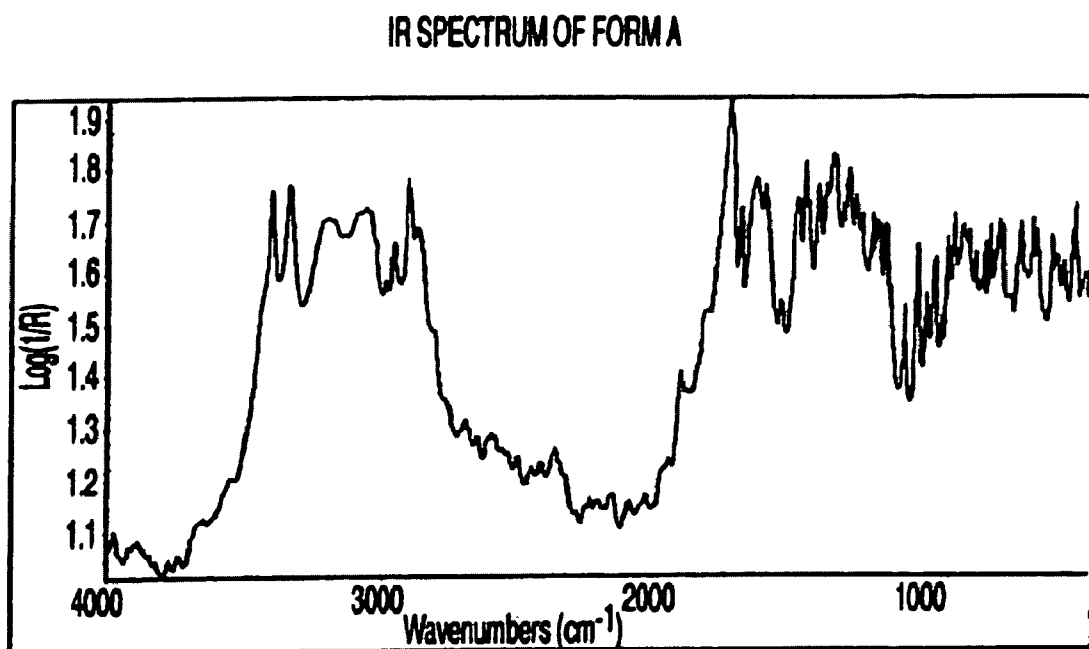


Fig. 2

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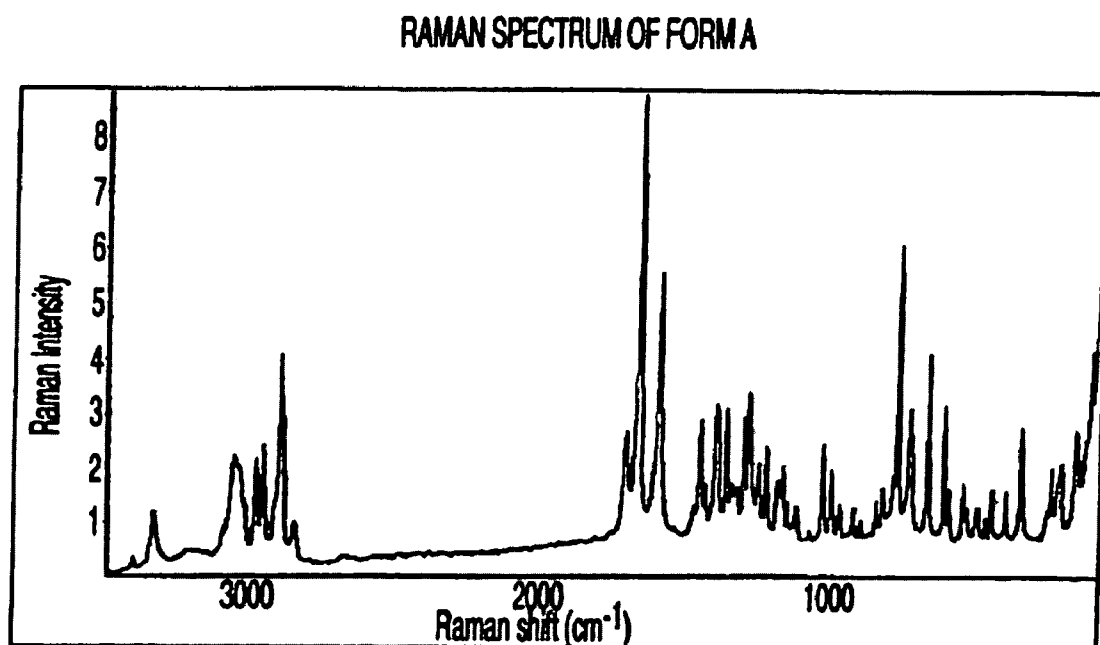


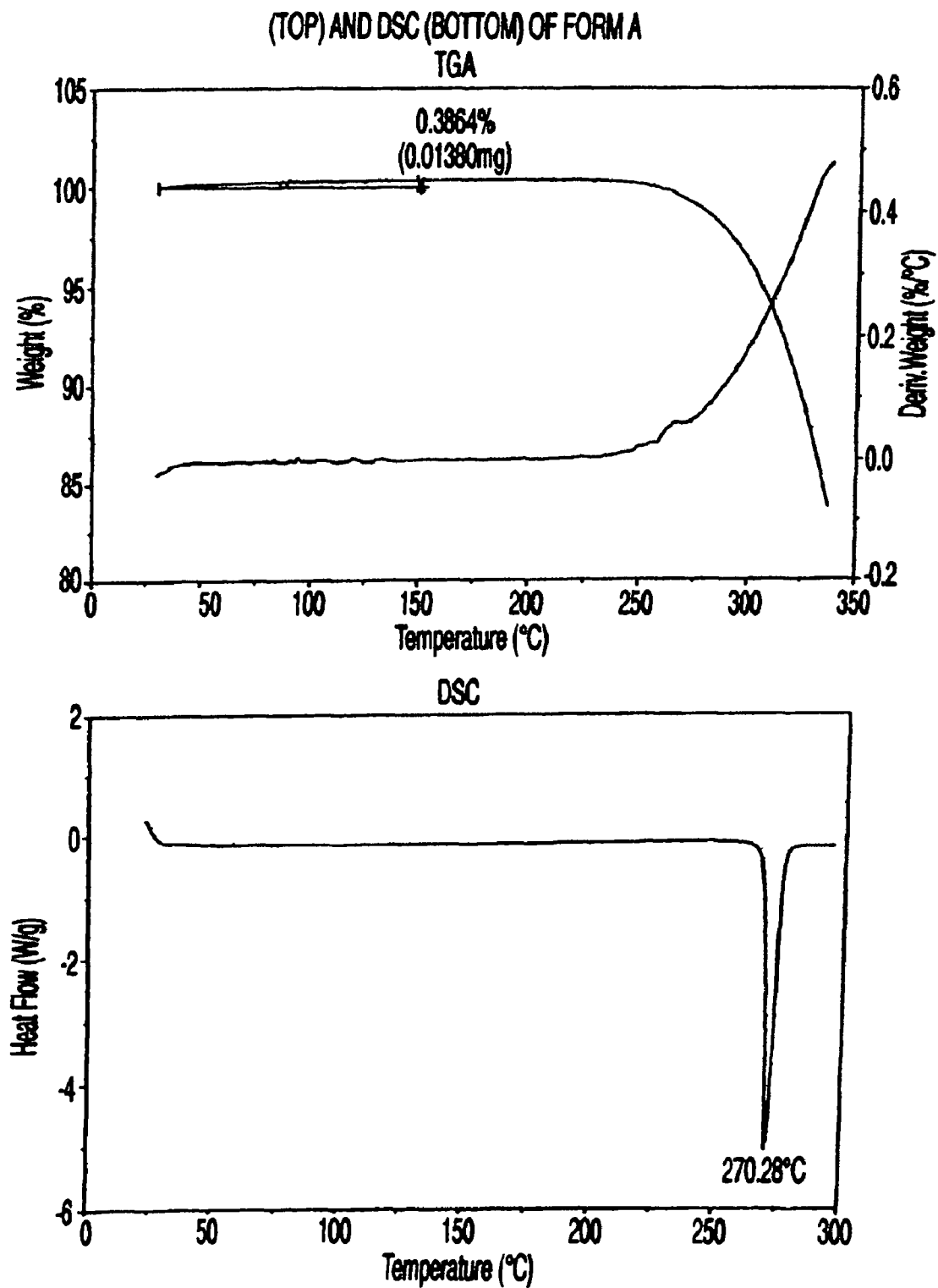
Fig. 3

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*Fig. 4*

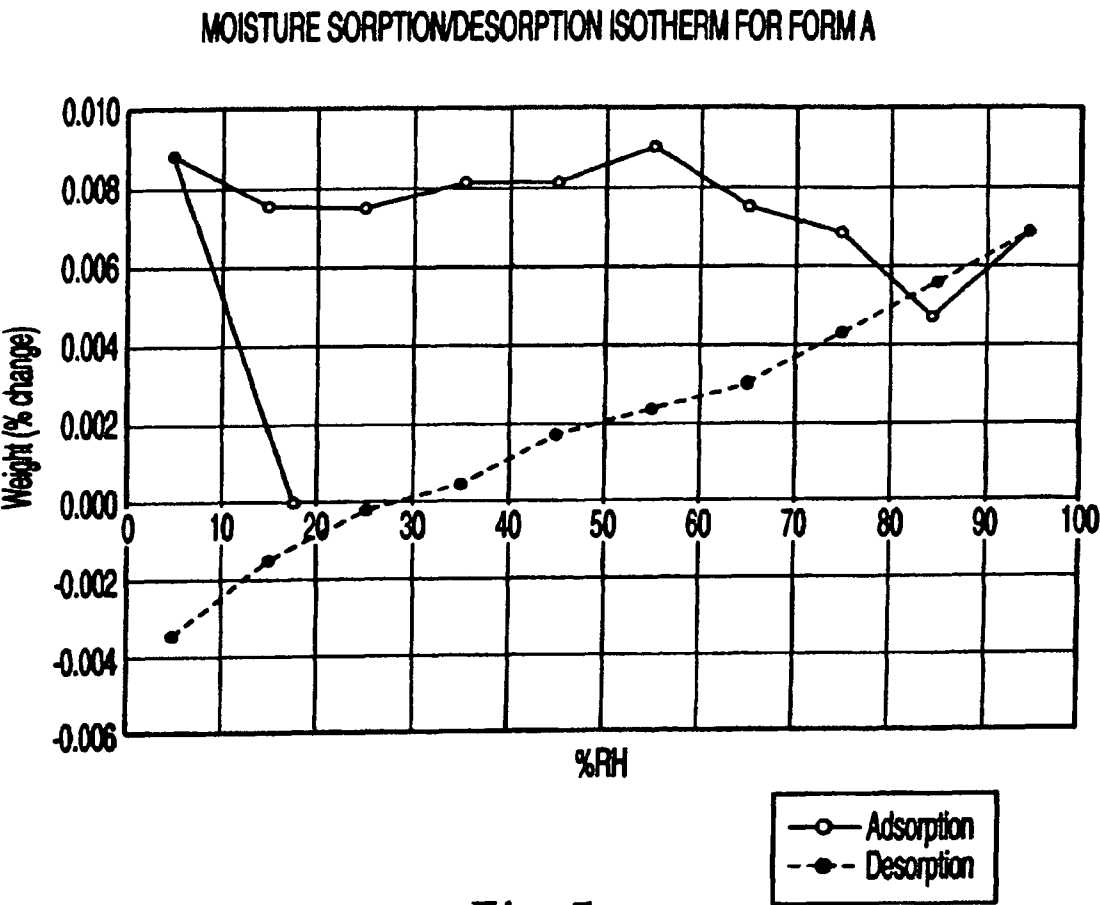


Fig. 5

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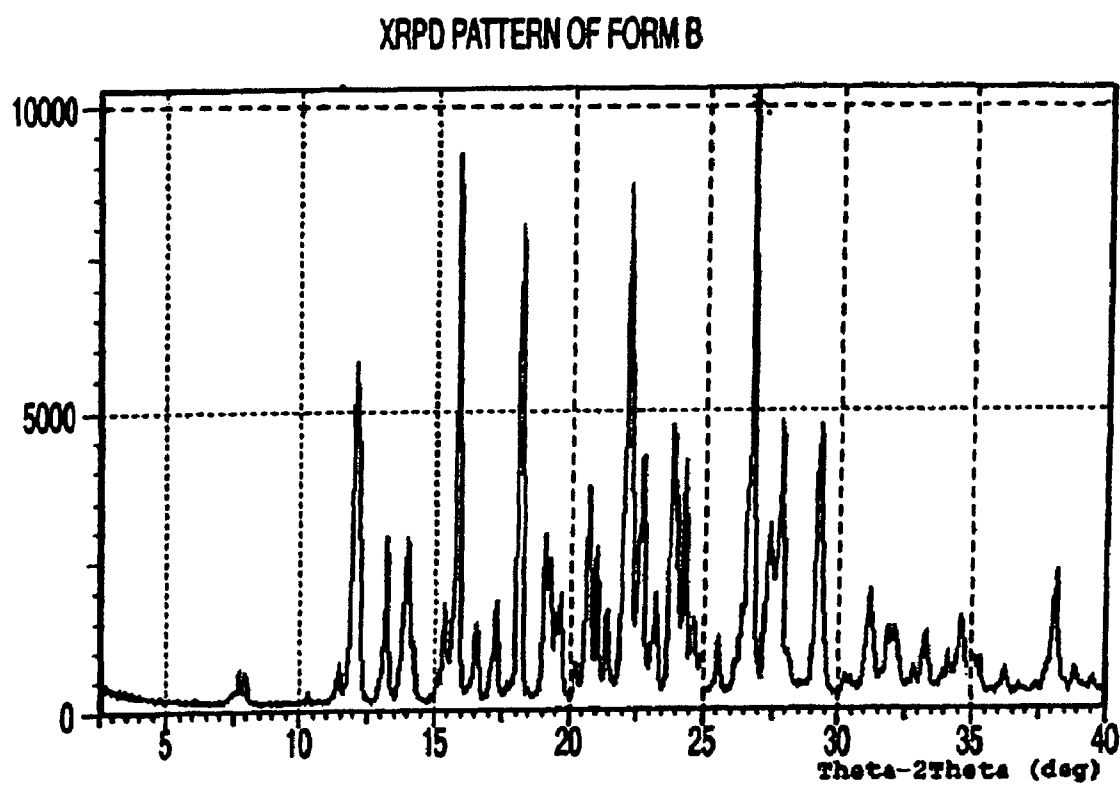


Fig. 6

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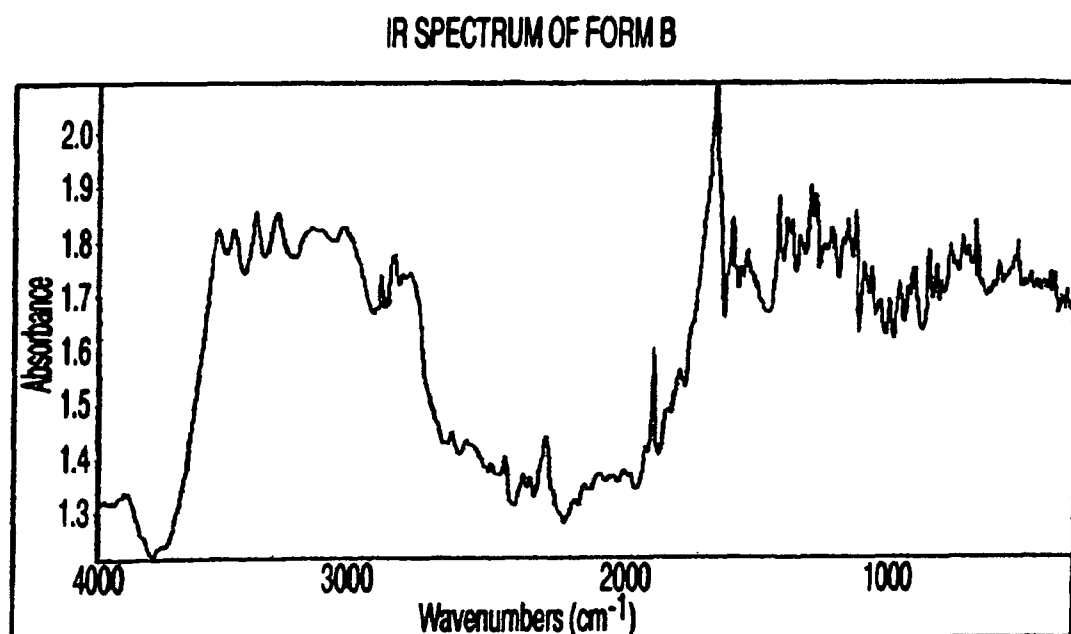


Fig. 7

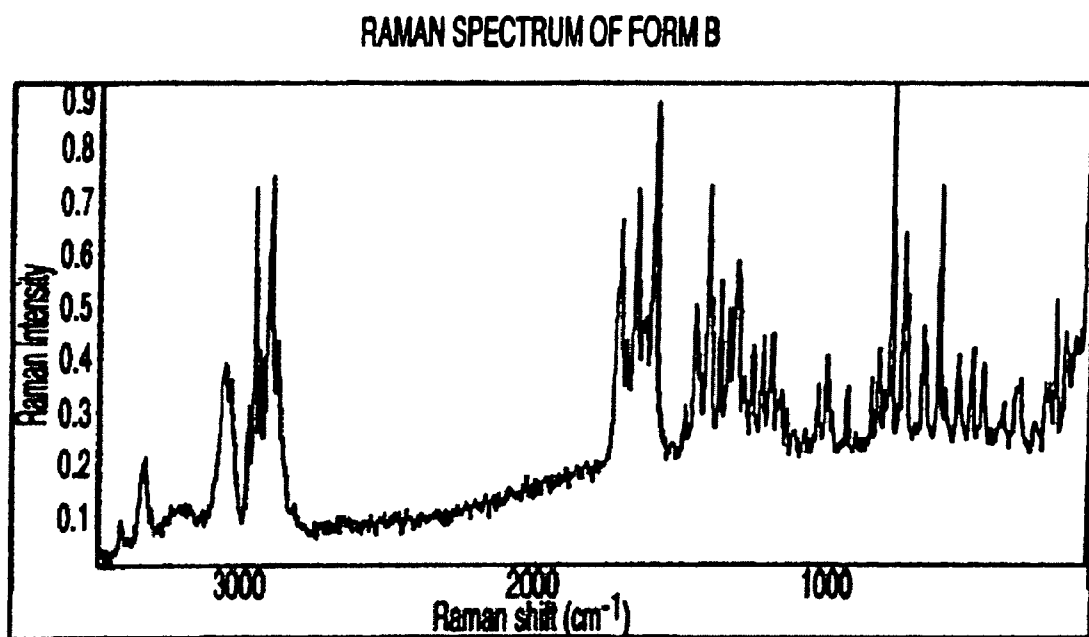


Fig. 8

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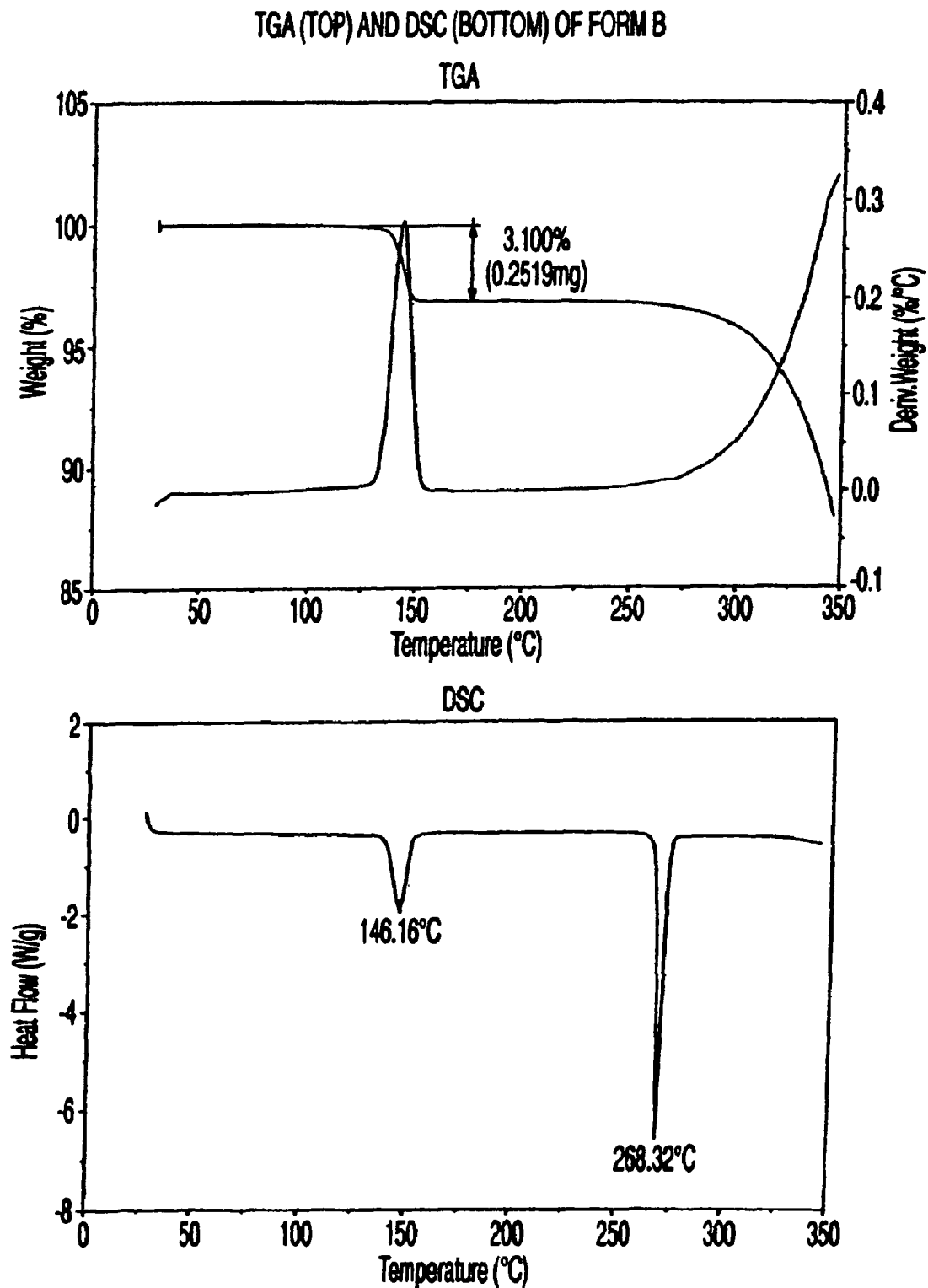


Fig. 9

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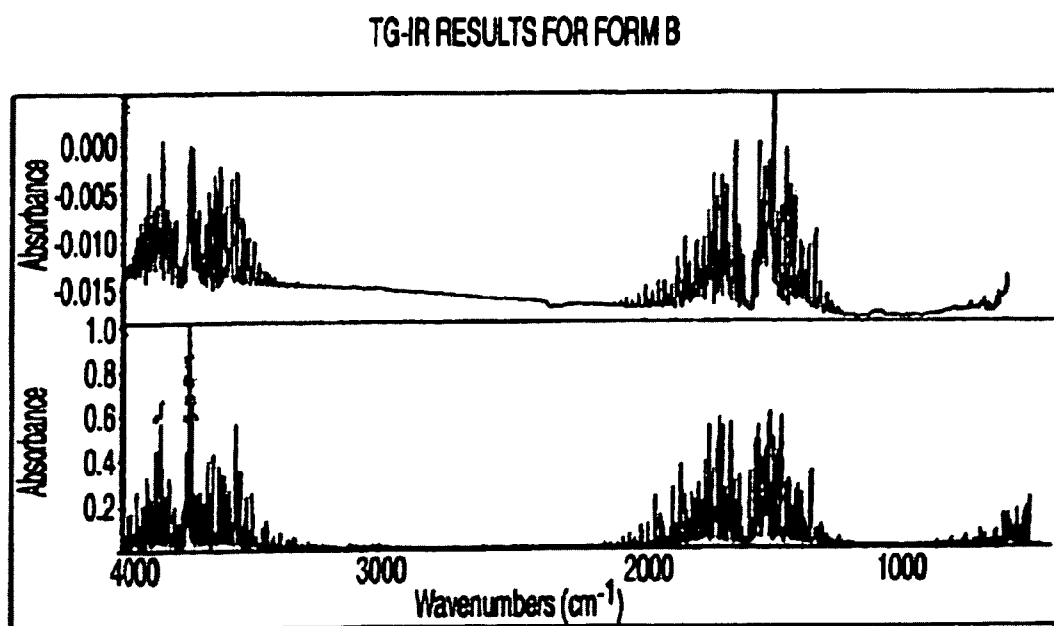
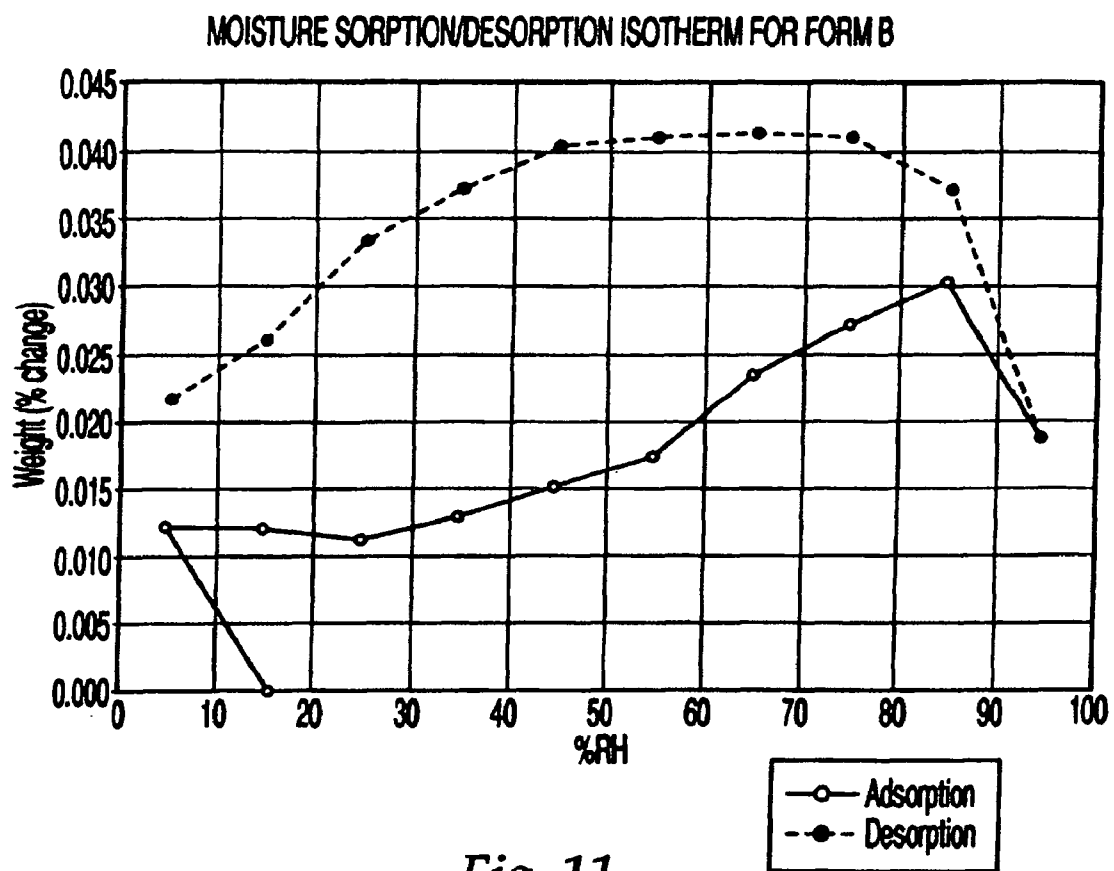


Fig. 10



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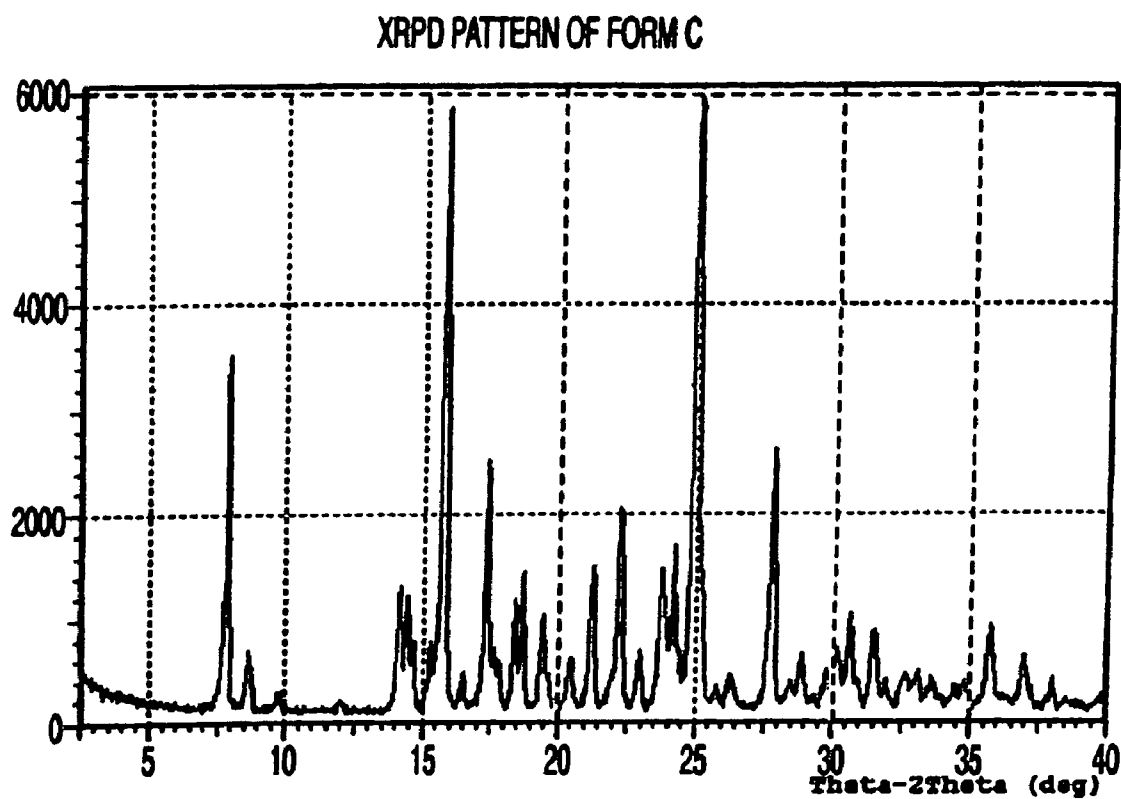


Fig. 12

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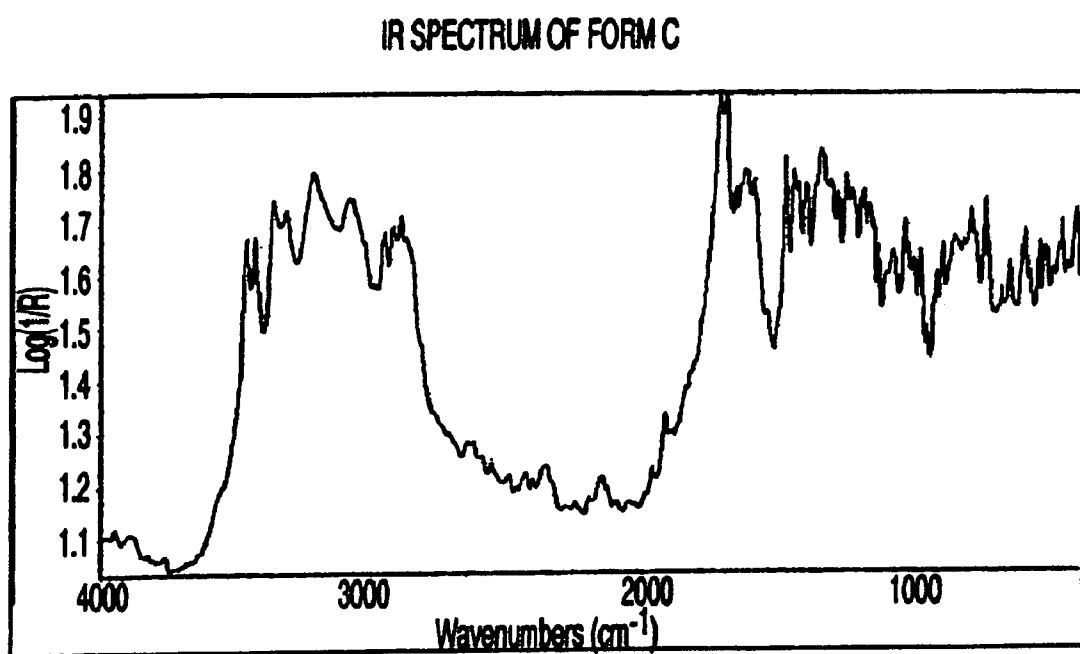


Fig. 13

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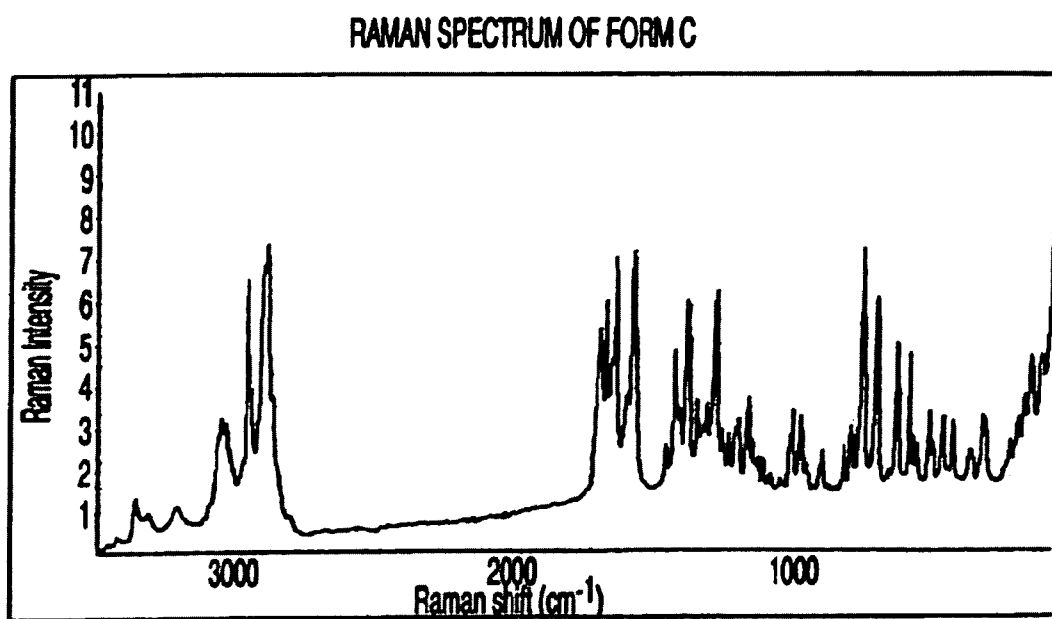
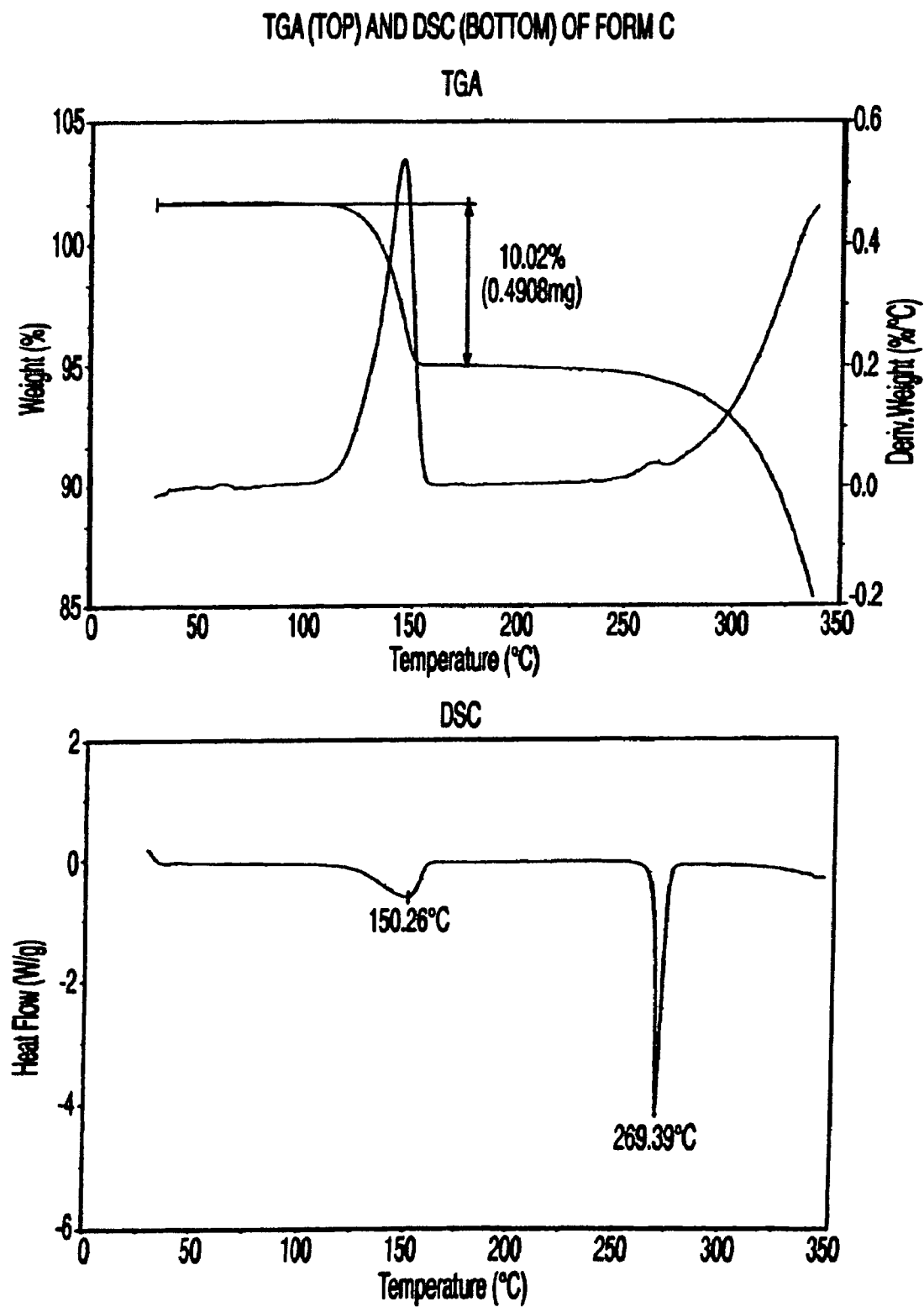


Fig. 14

*Fig. 15*

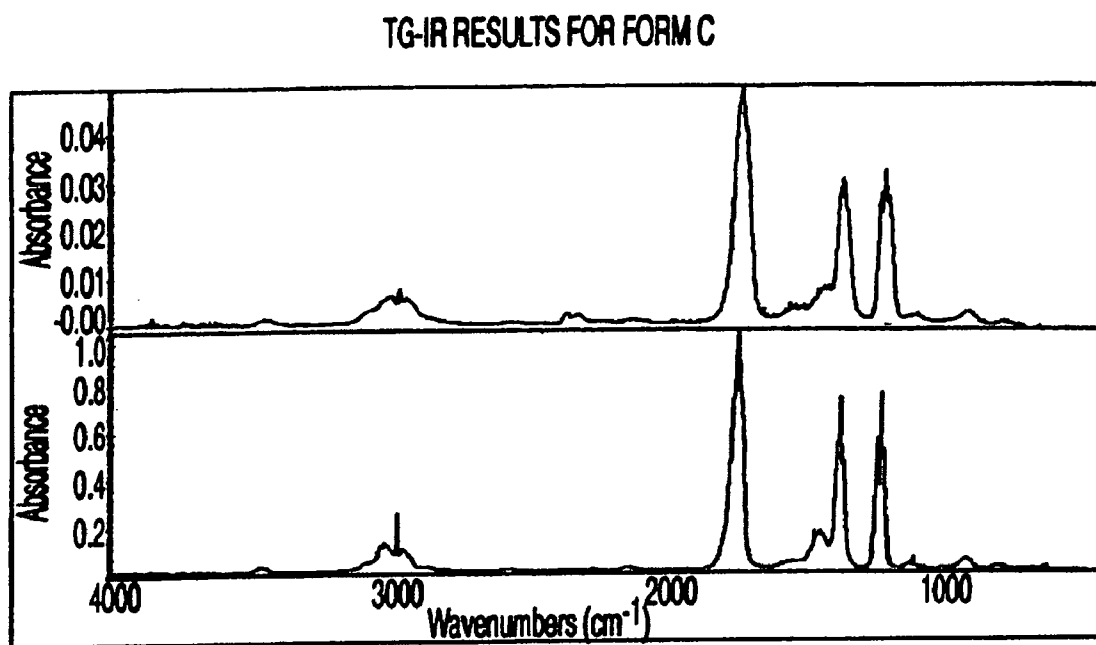


Fig. 16

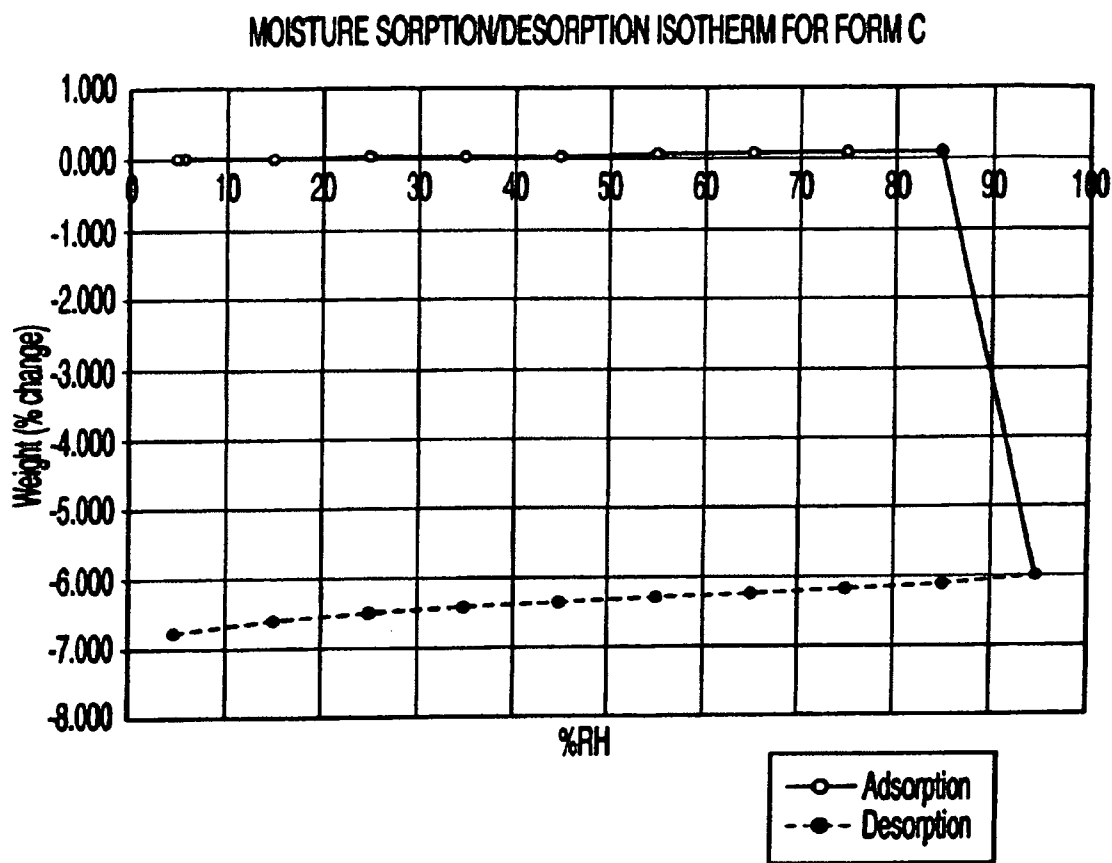


Fig. 17

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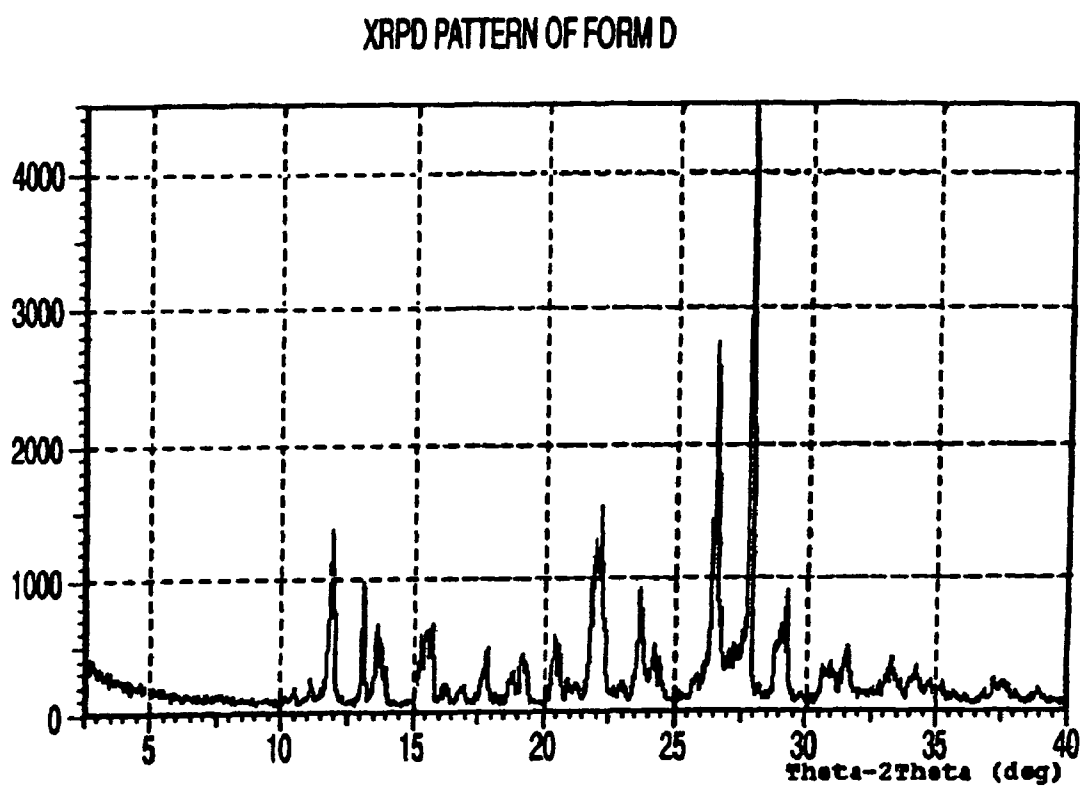


Fig. 18

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IR SPECTRUM OF FORM D

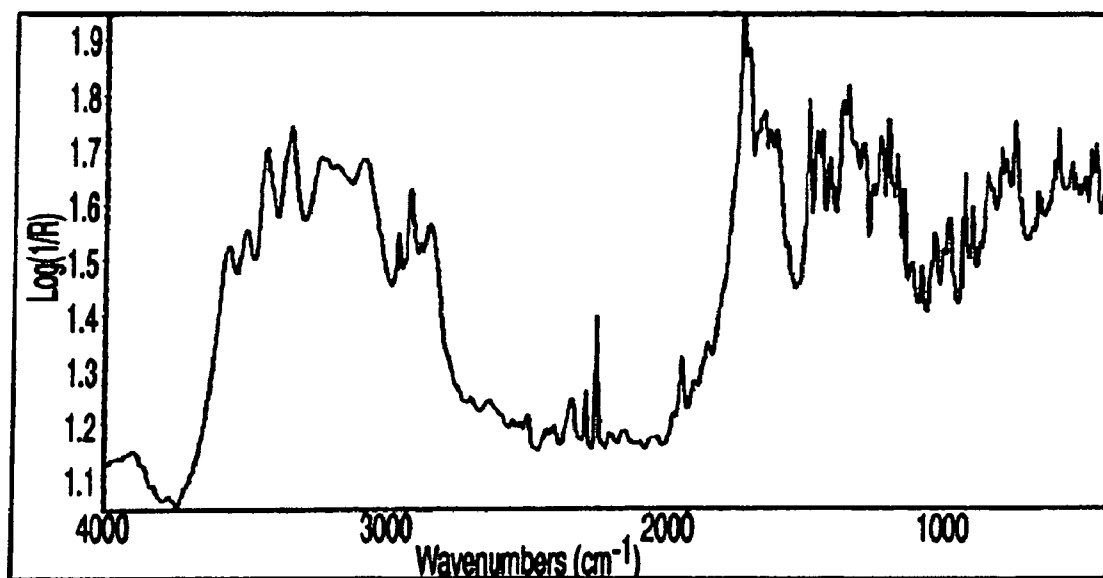


Fig. 19

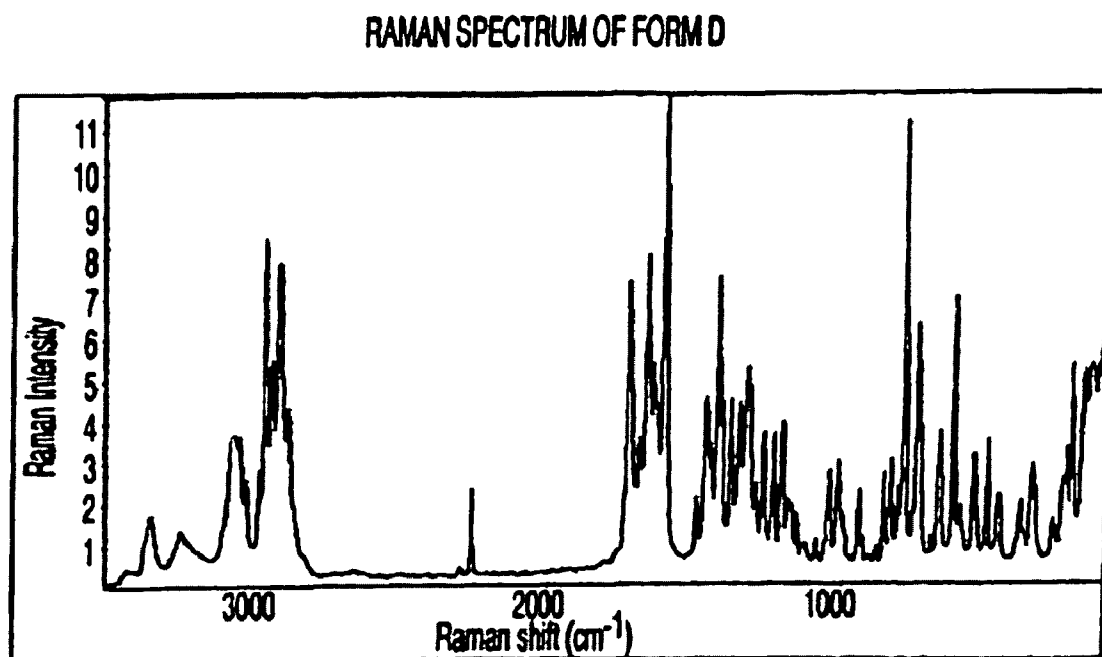
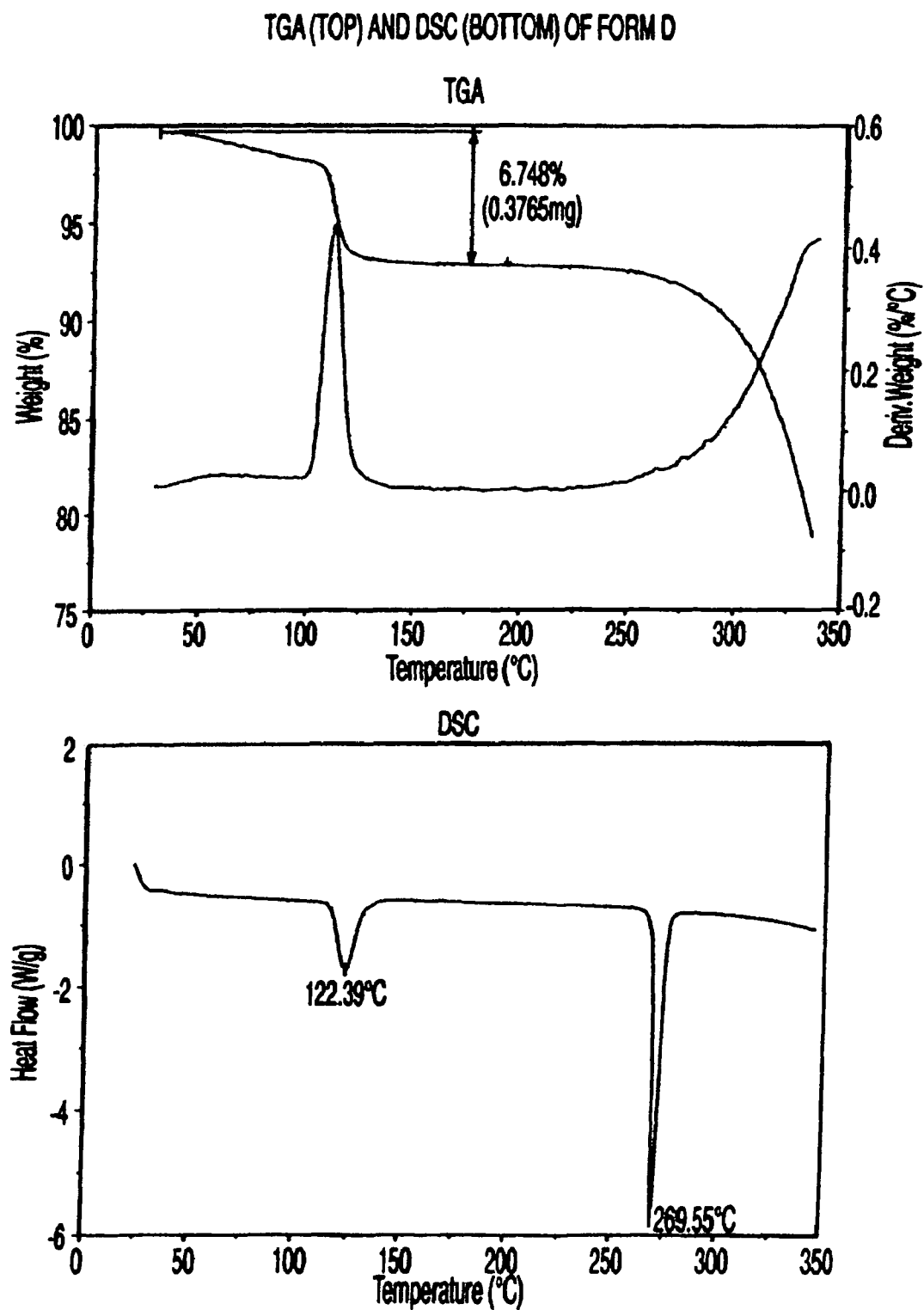
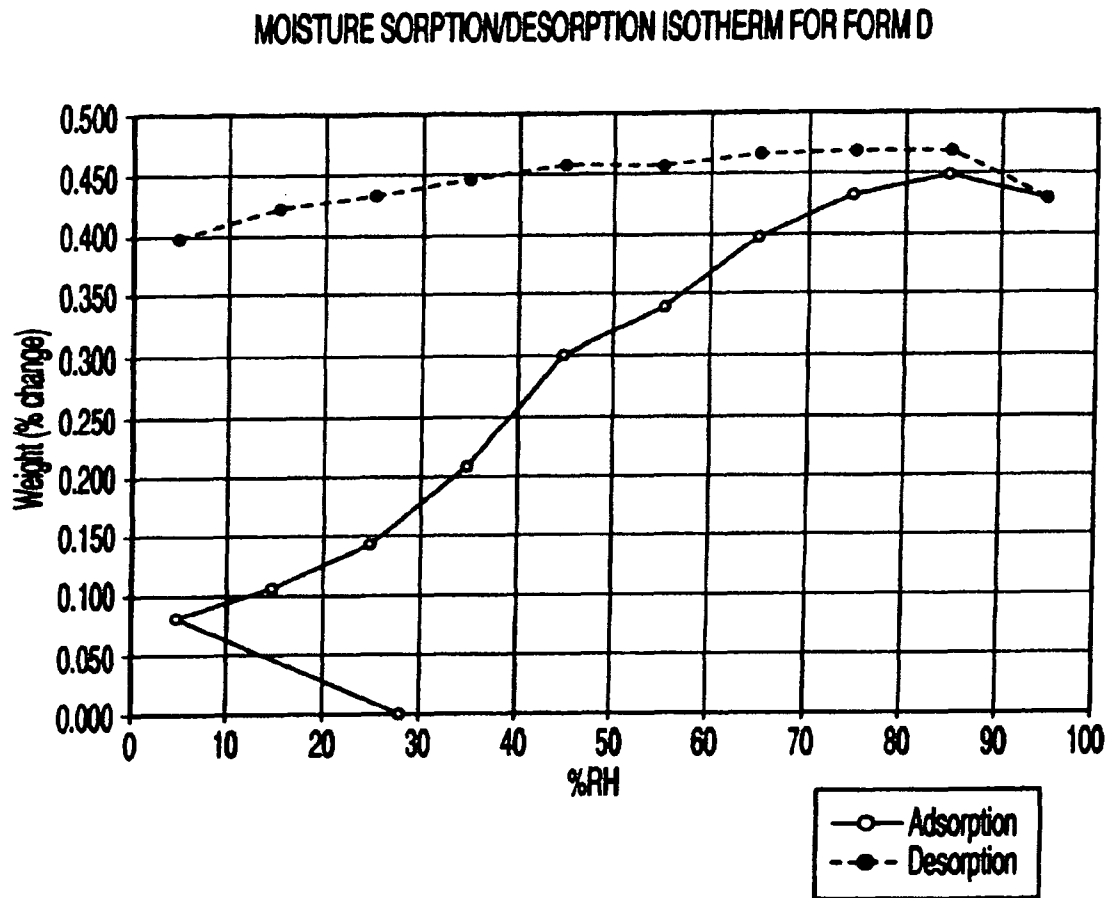


Fig. 20



*Fig. 22*

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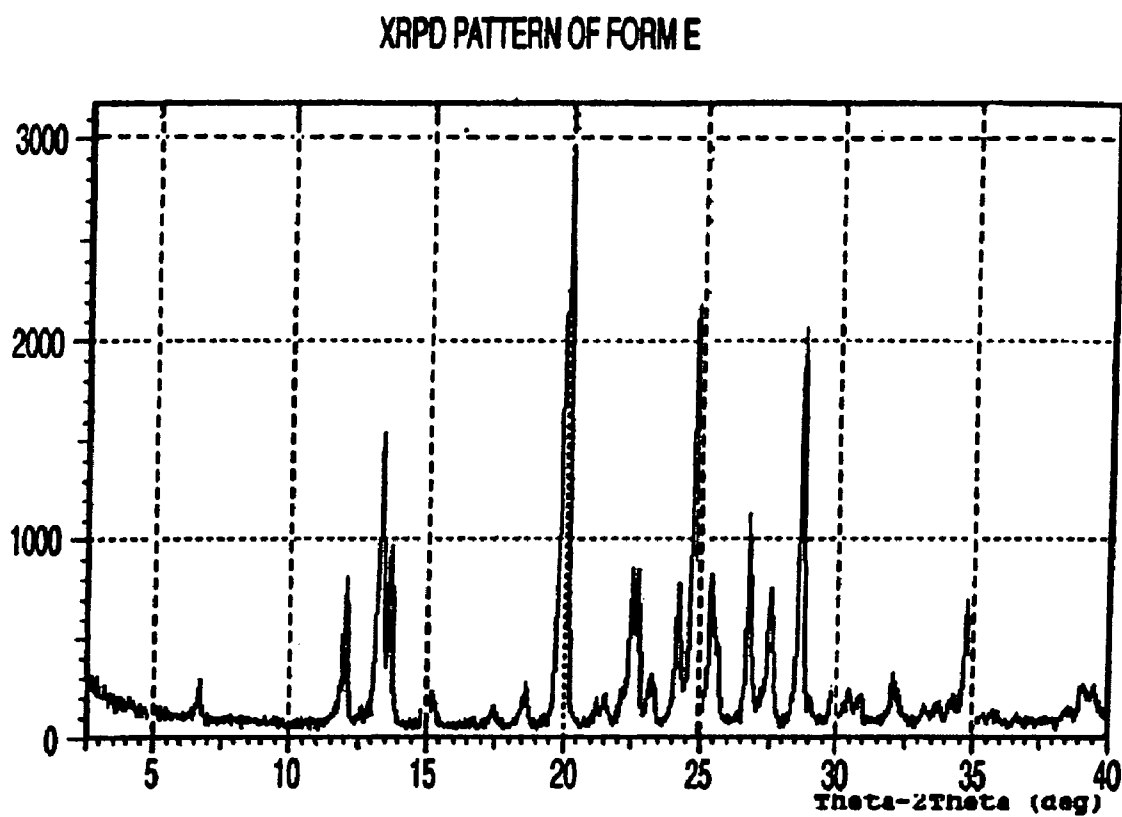


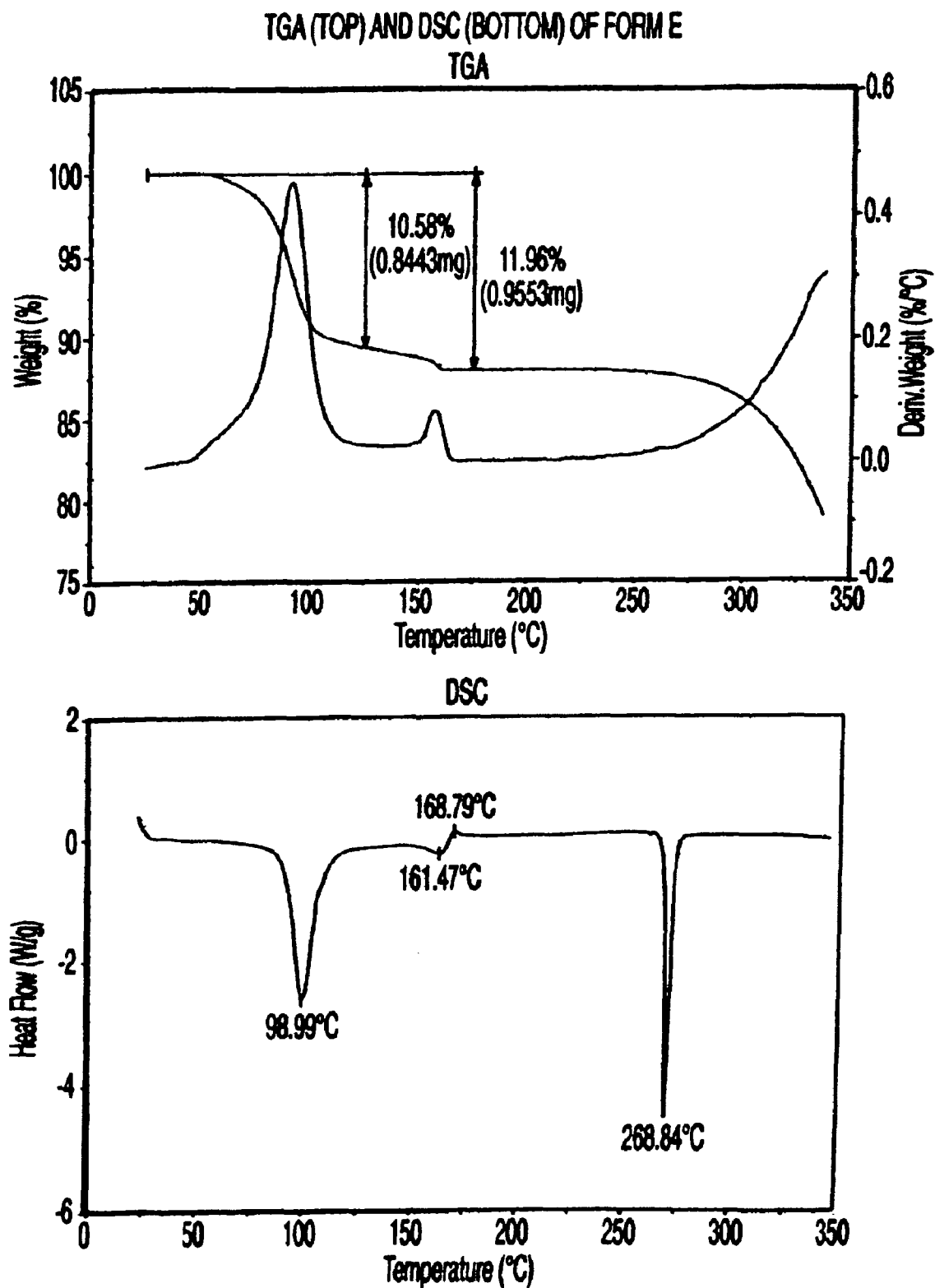
Fig. 23

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*Fig. 24*

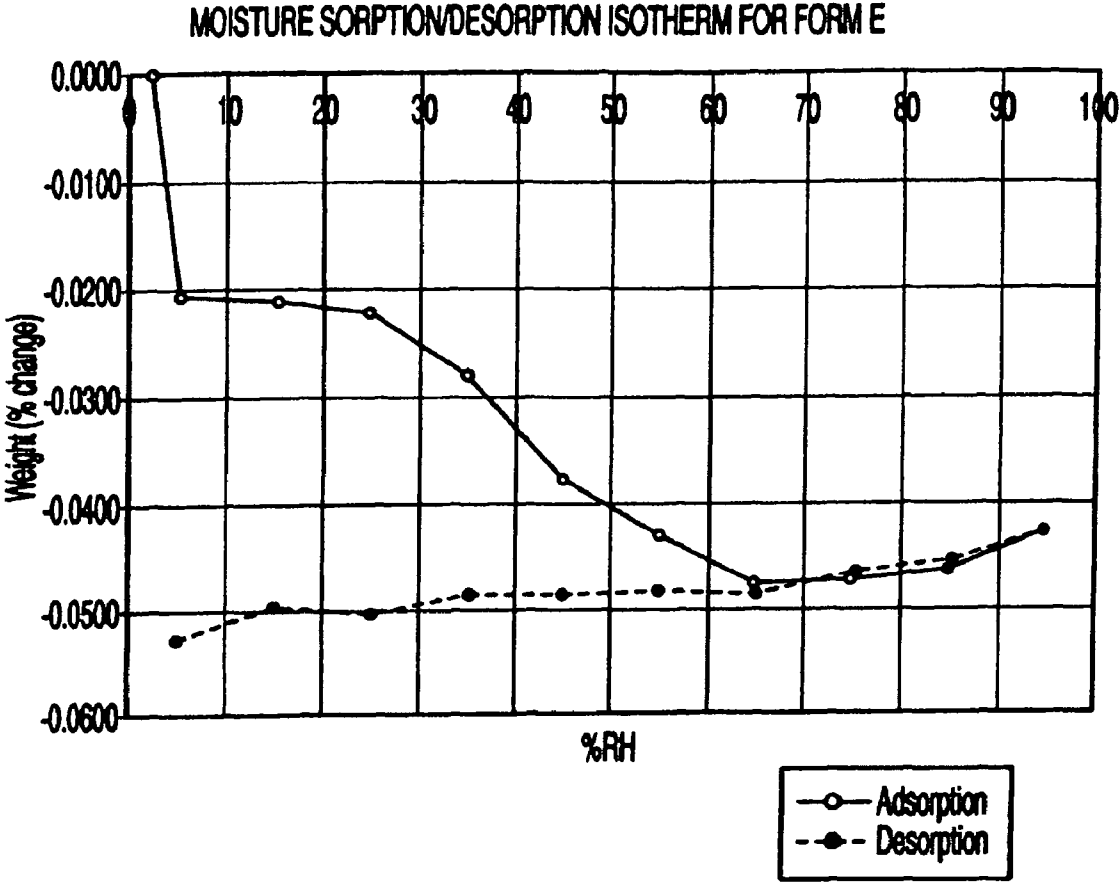


Fig. 25

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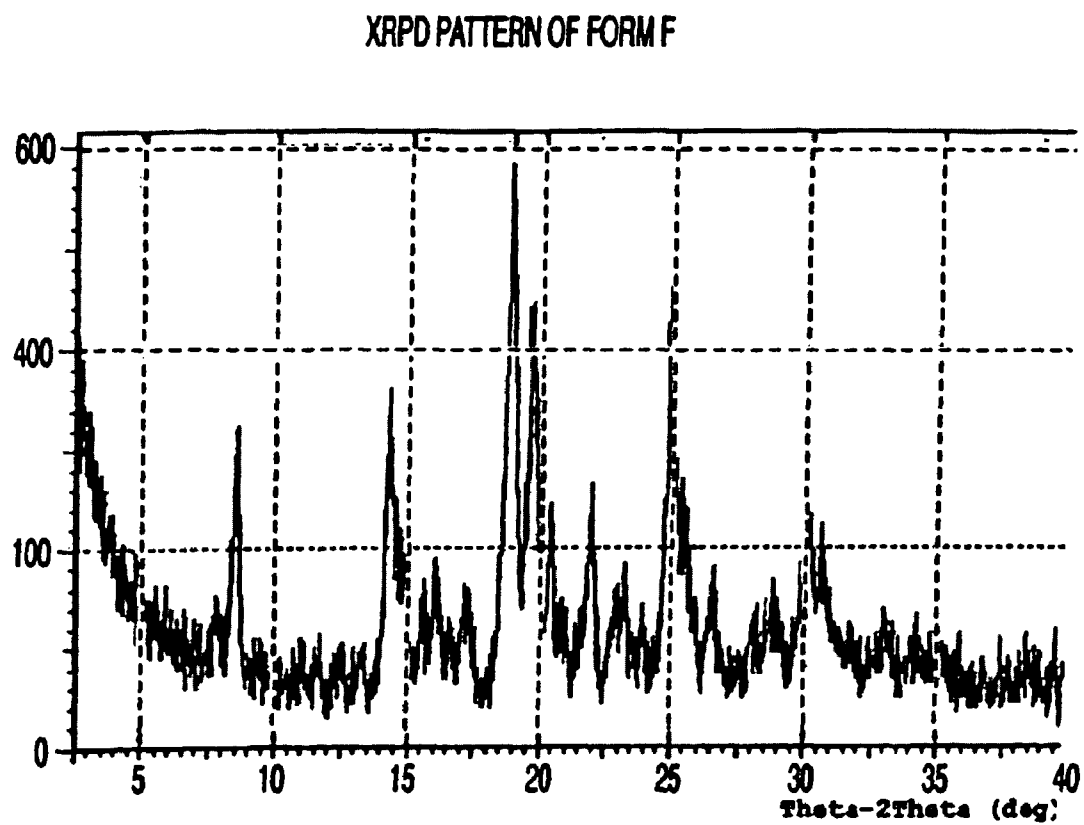


Fig. 26

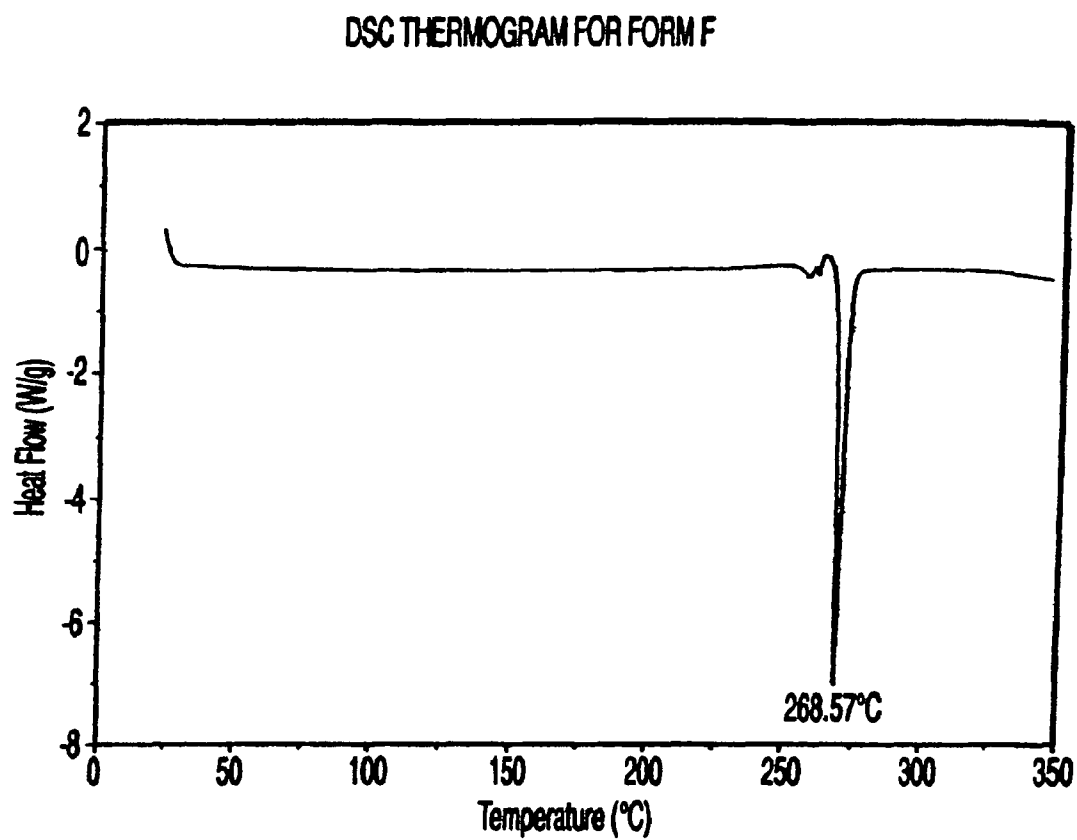


Fig. 27

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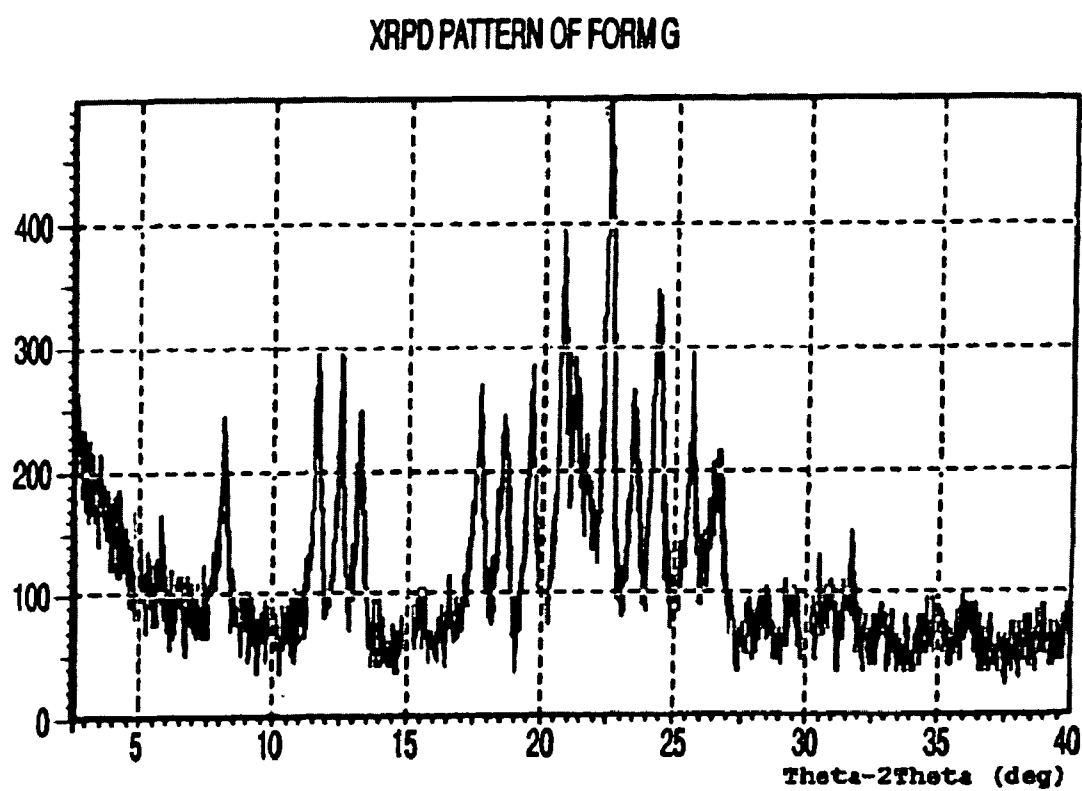


Fig. 28

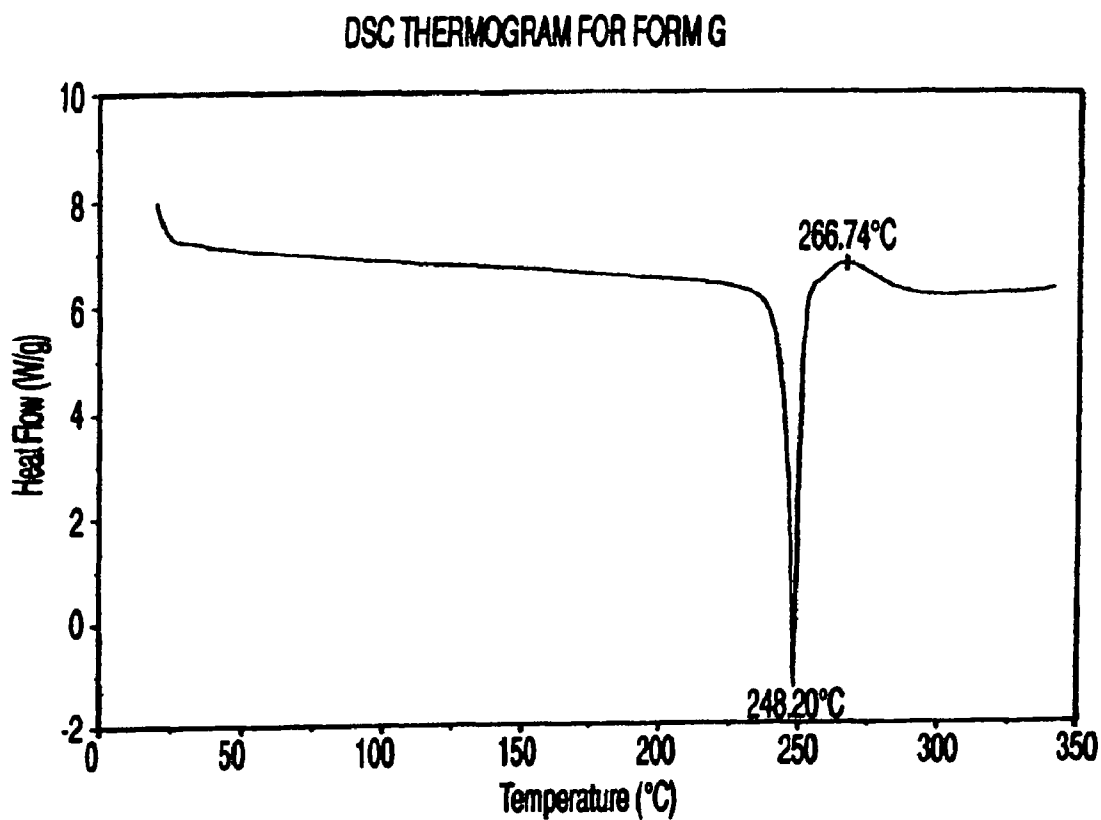


Fig. 29

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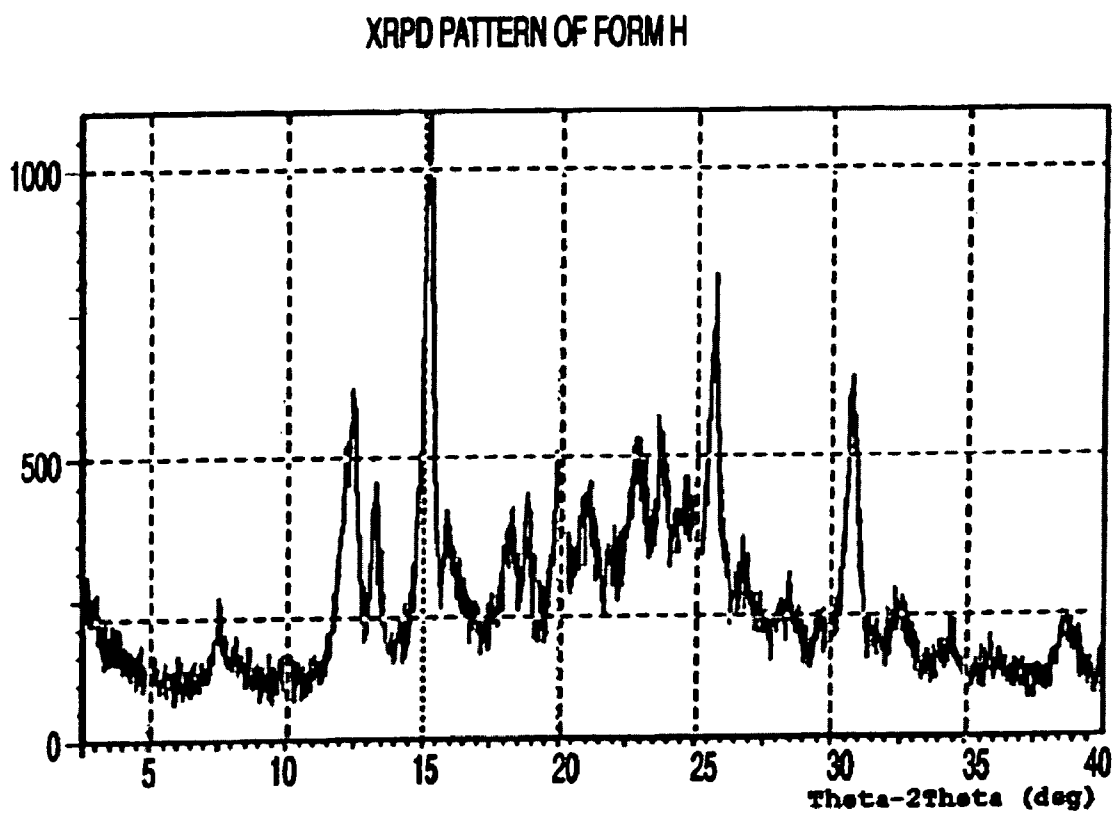


Fig. 30

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TGA (TOP) AND DSC (BOTTOM) OF FORM H

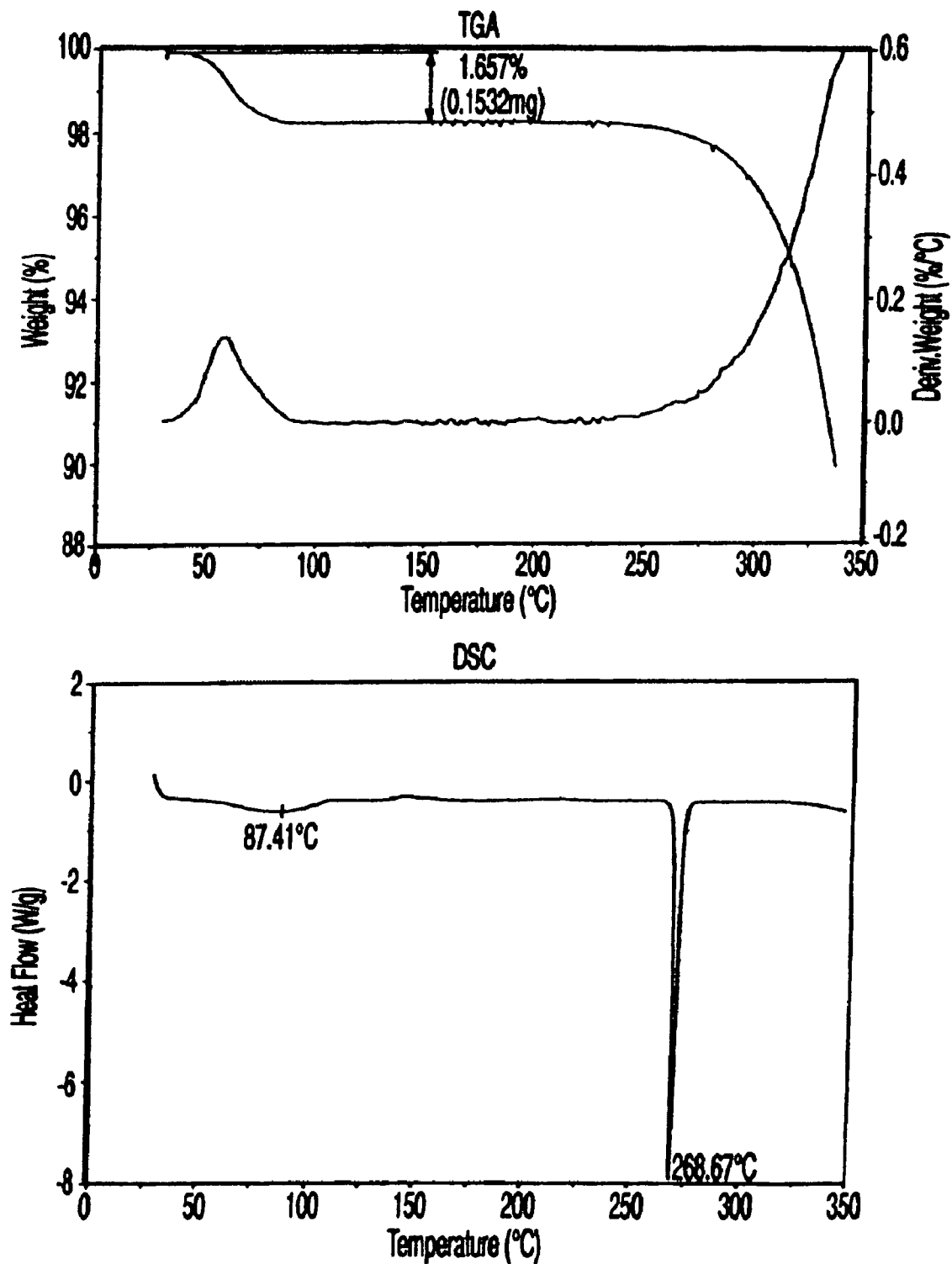


Fig. 31

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XRPD PATTERN OF POLYMORPH B

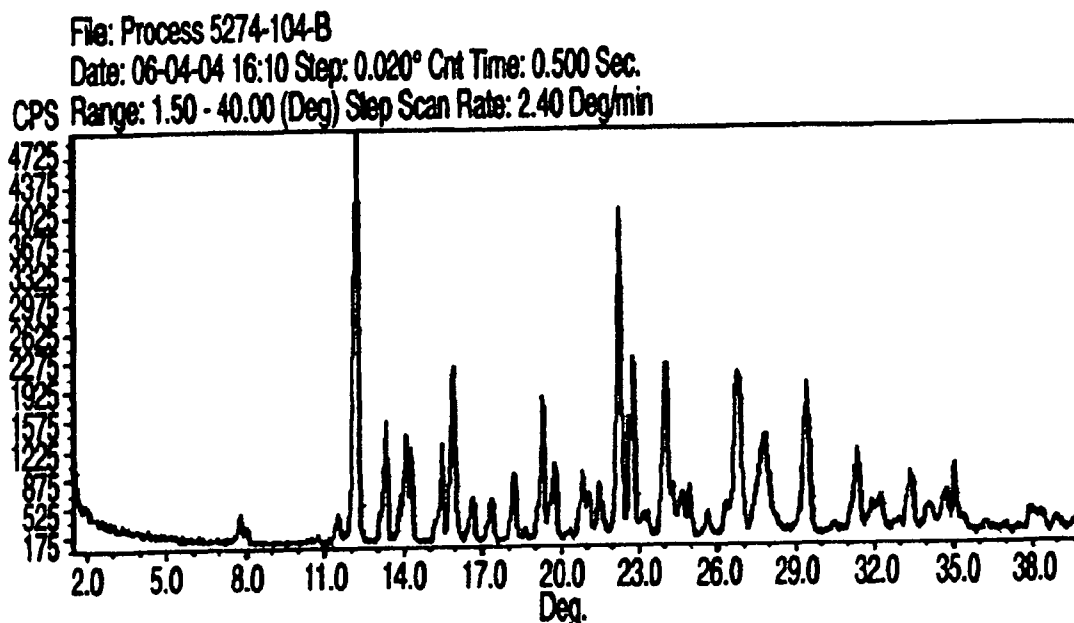


Fig. 32

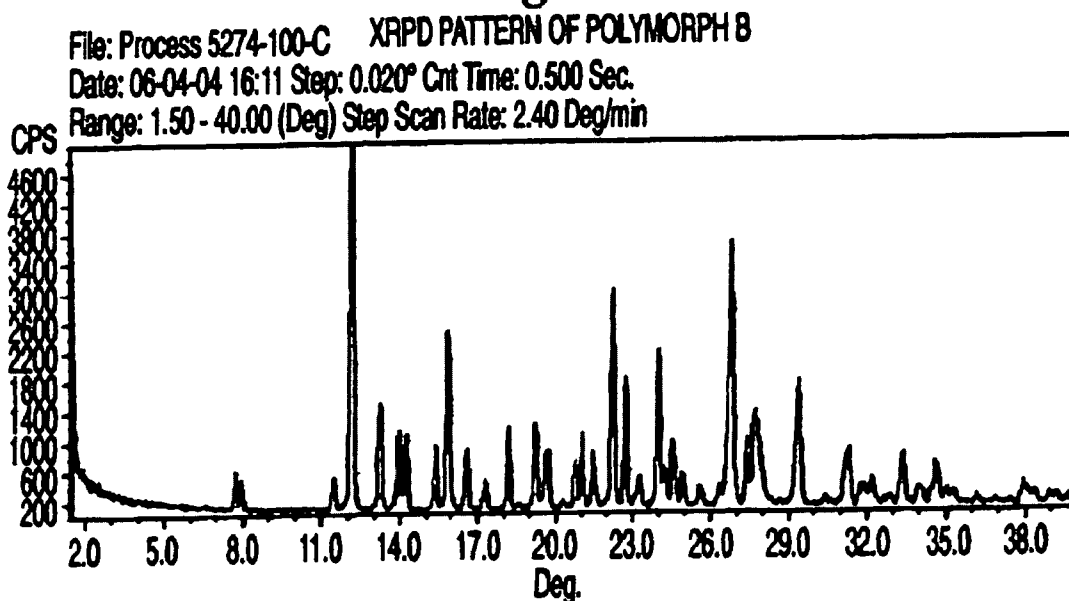


Fig. 33

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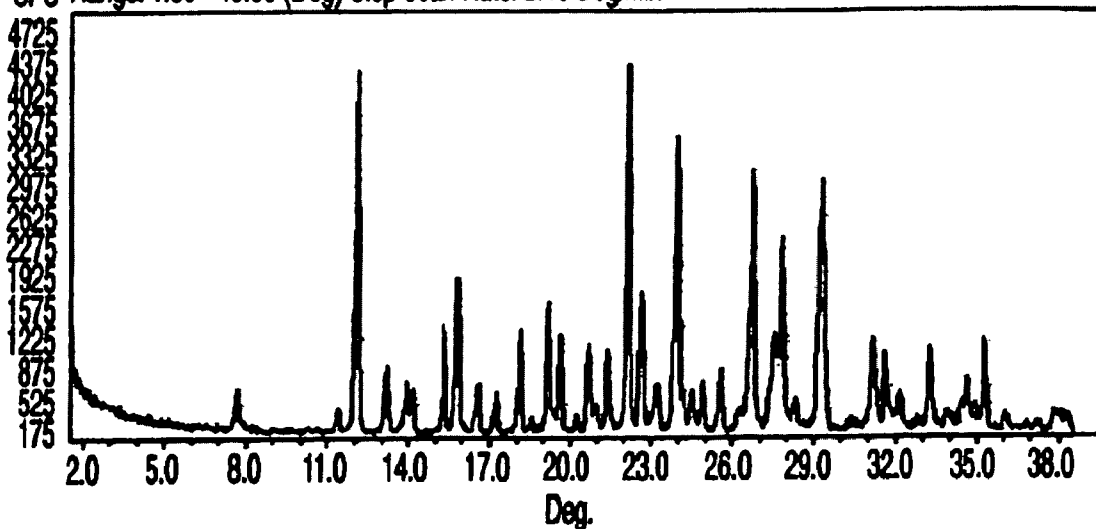
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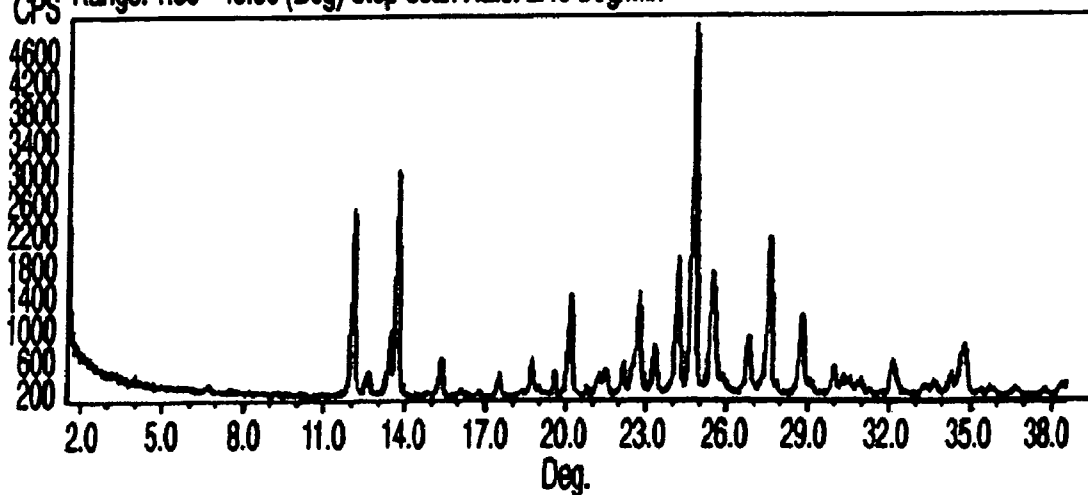
XRPD PATTERN OF POLYMORPH B

File: Process 5274-104-B
Date: 06-04-04 16:10 Step: 0.020° Cnt Time: 0.500 Sec.
Range: 1.50 - 40.00 (Deg) Step Scan Rate: 2.40 Deg/min

*Fig. 34*

XRPD PATTERN OF POLYMORPH E

File: Process 5274-100-C
Date: 06-04-04 16:11 Step: 0.020° Cnt Time: 0.500 Sec.
Range: 1.50 - 40.00 (Deg) Step Scan Rate: 2.40 Deg/min

*Fig. 35*

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XRPD PATTERN OF POLYMORPH MIXTURE

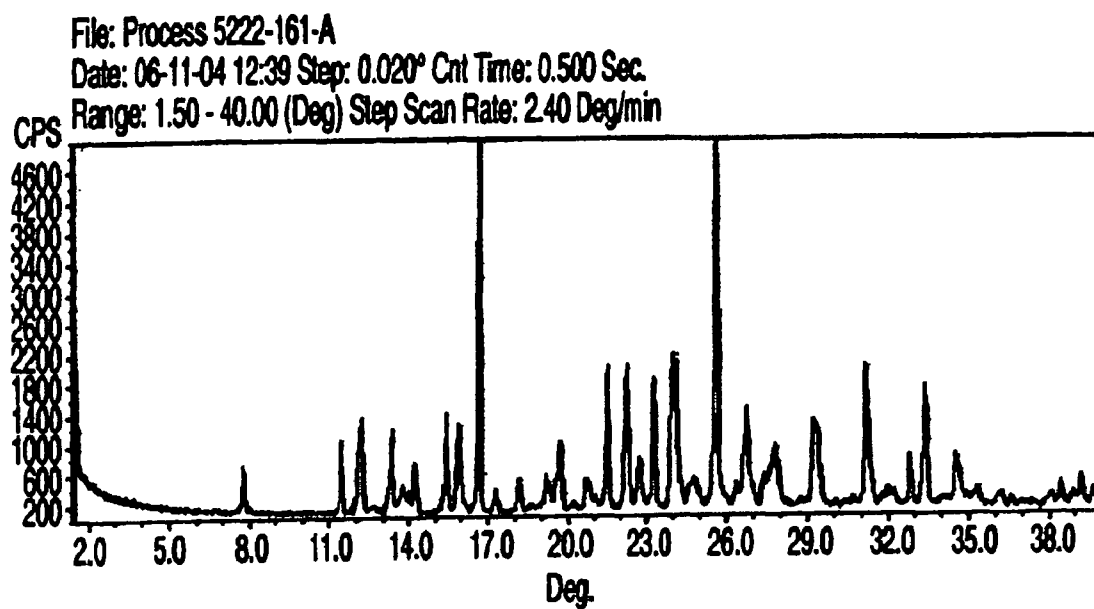


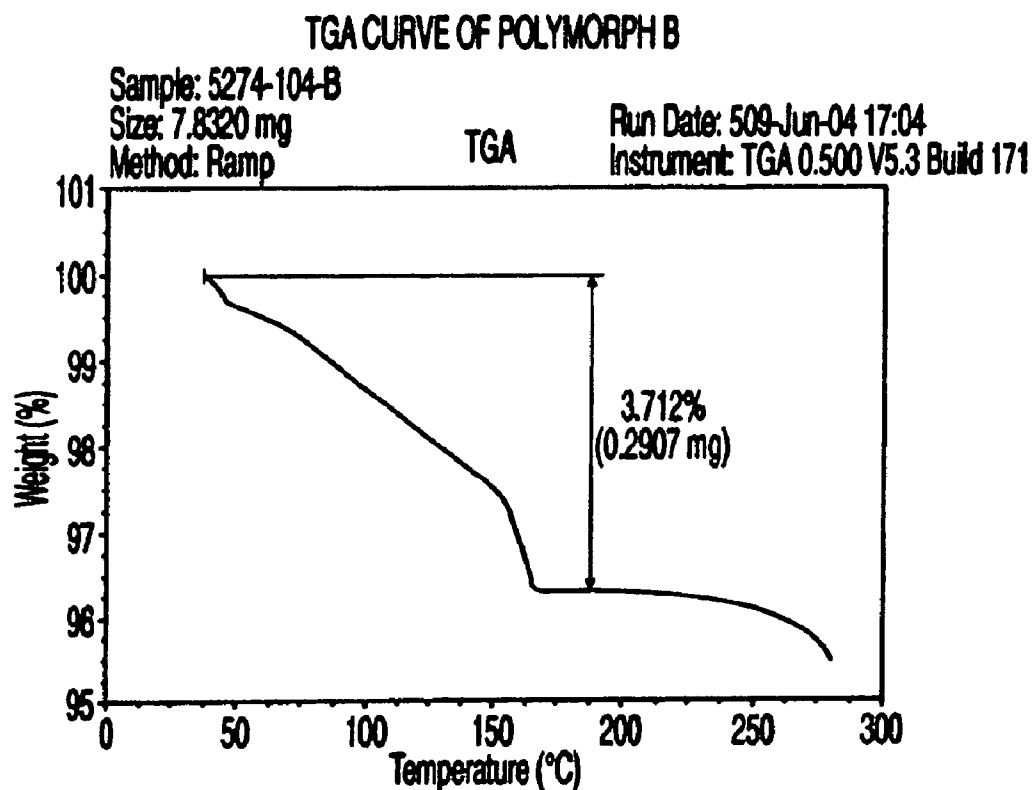
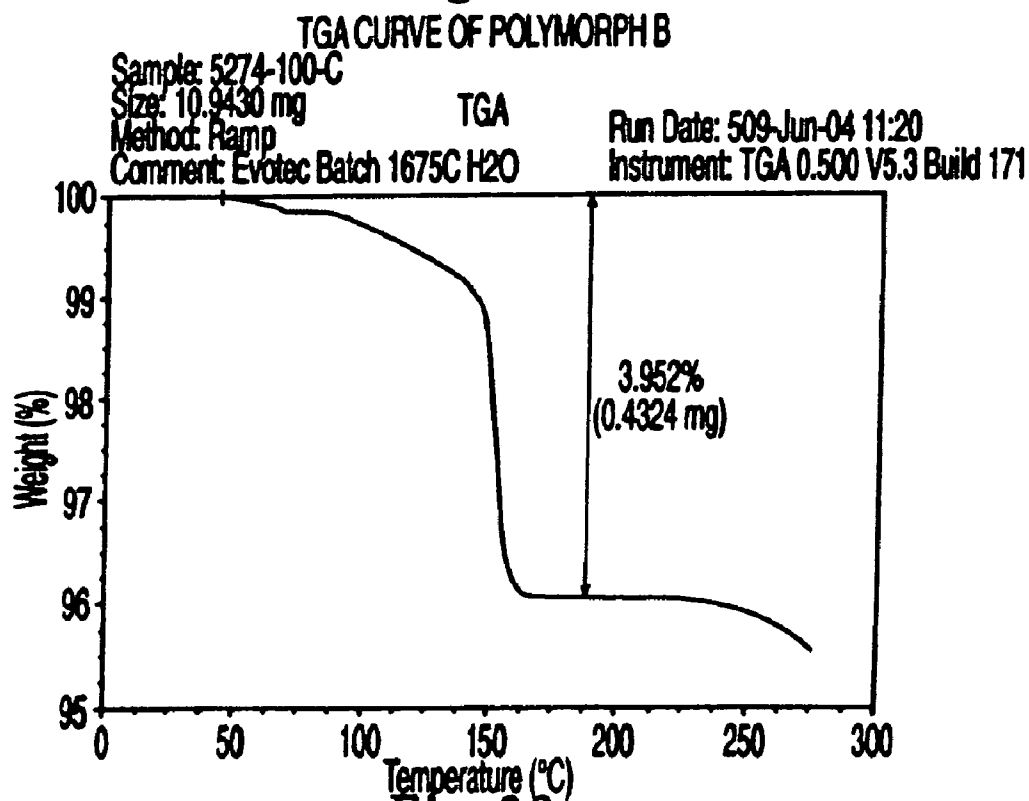
Fig. 36

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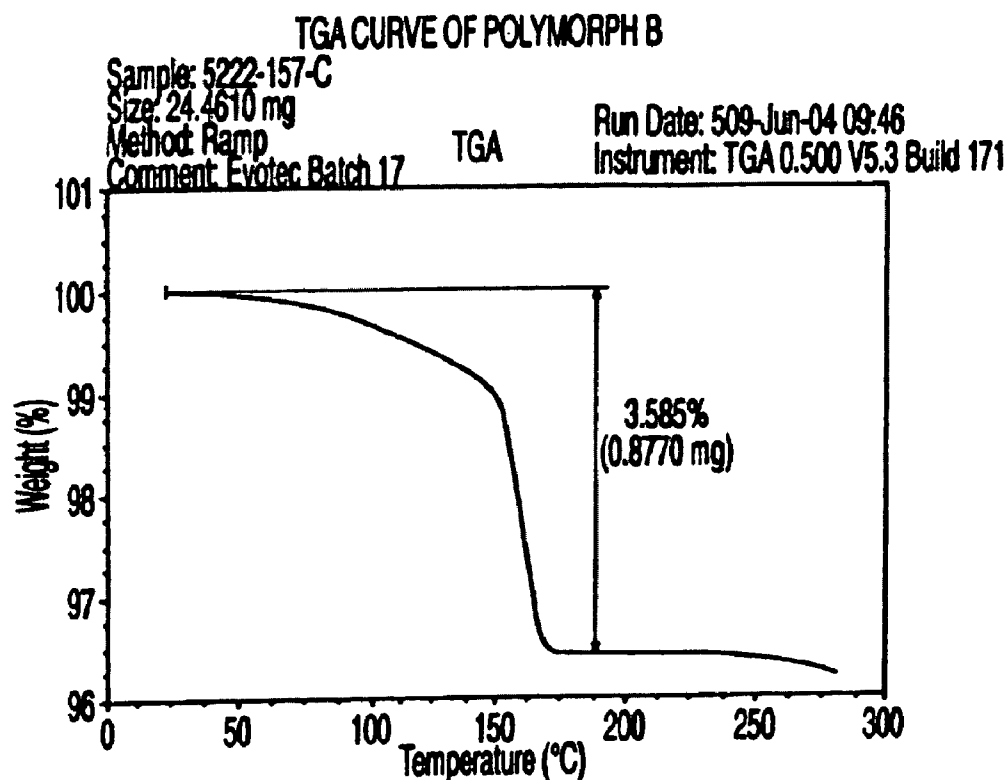
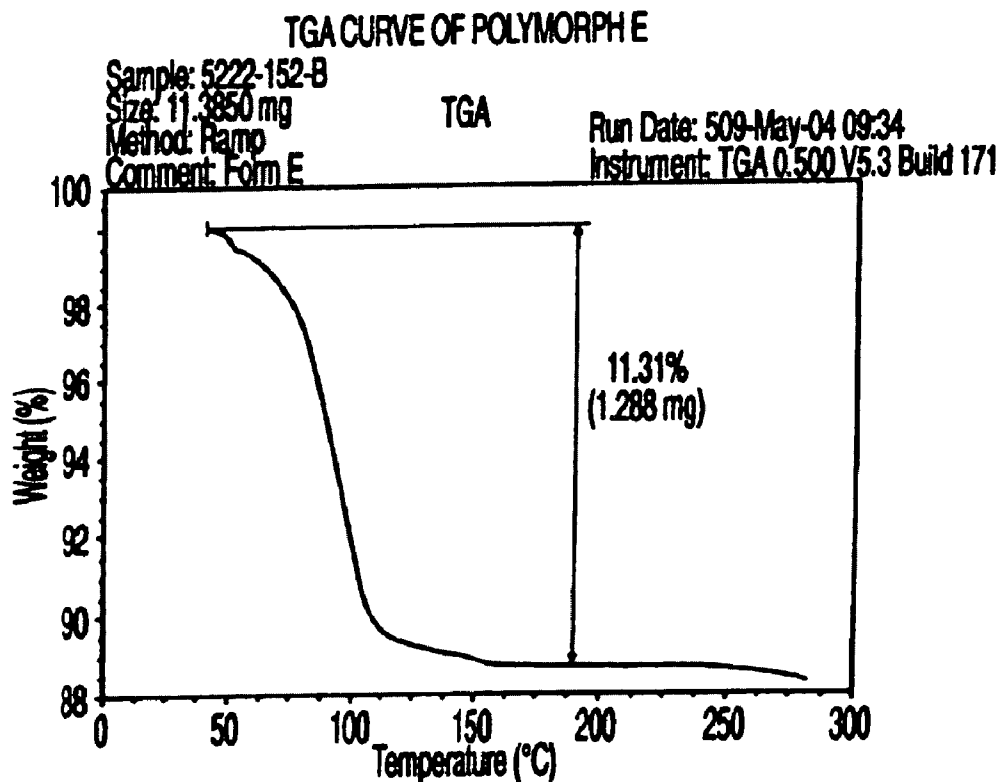
*Fig. 37**Fig. 38*

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*Fig. 39**Fig. 40*

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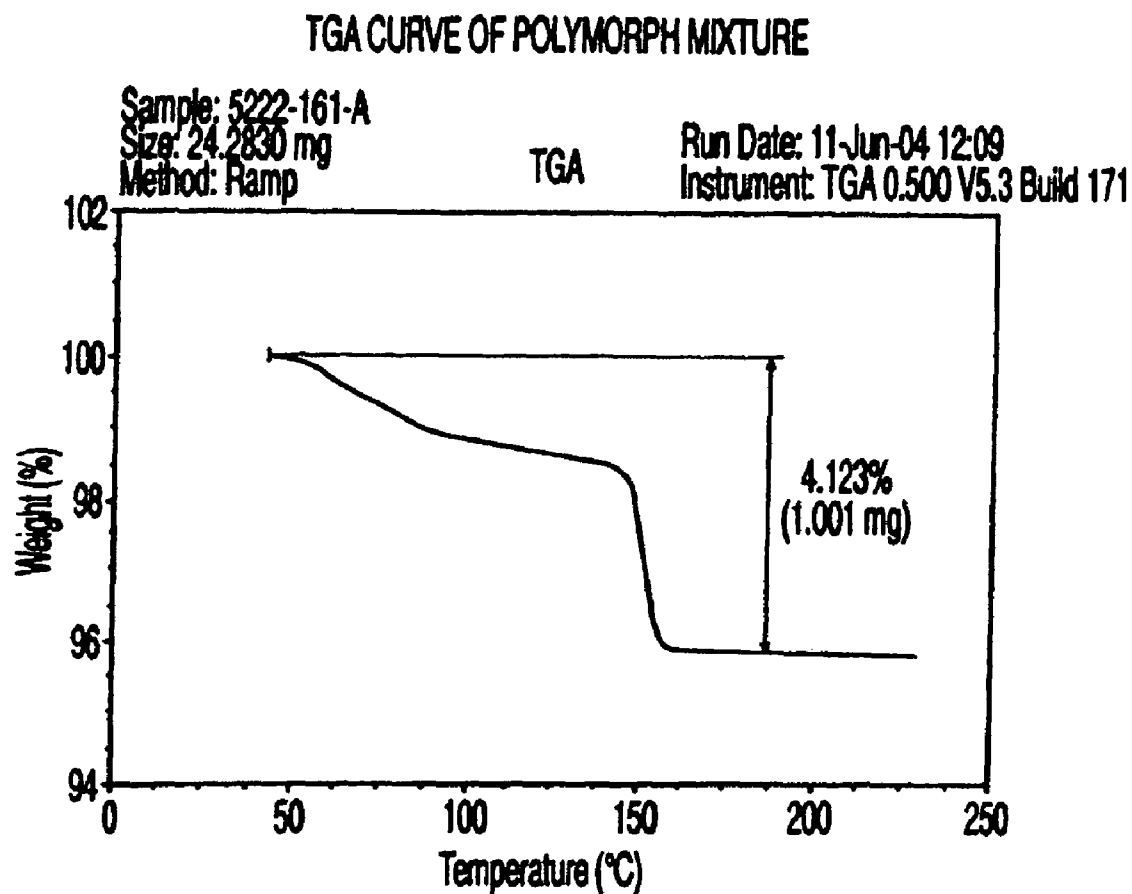


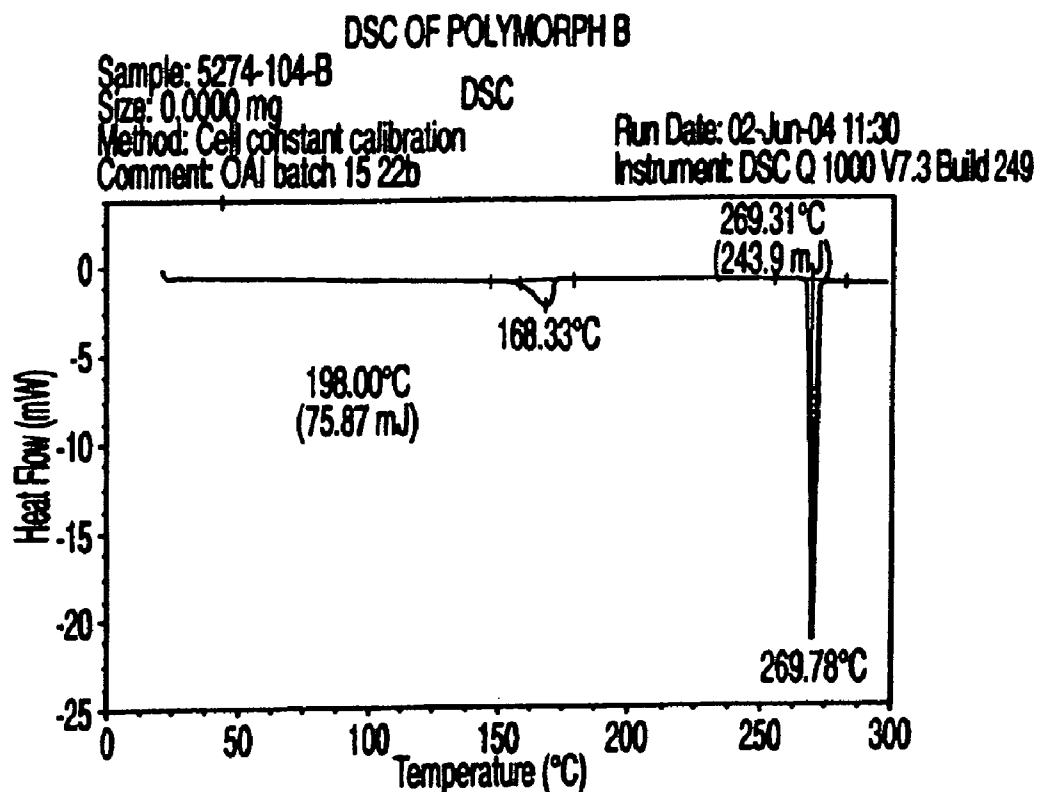
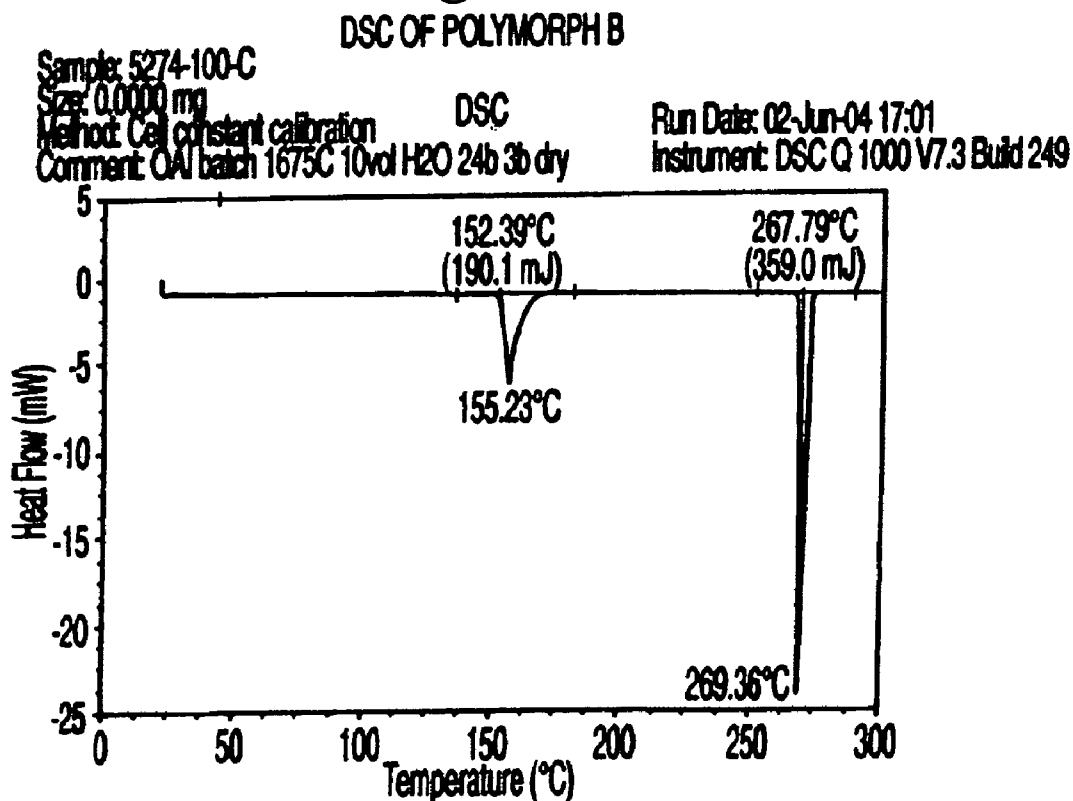
Fig. 41

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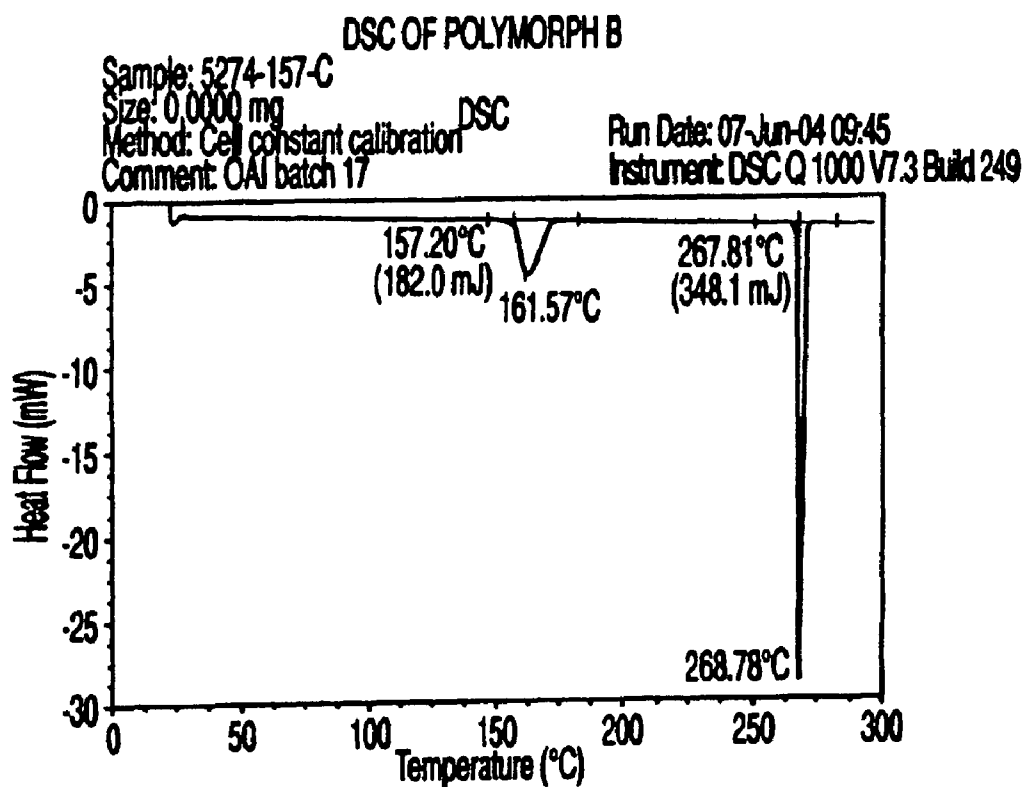
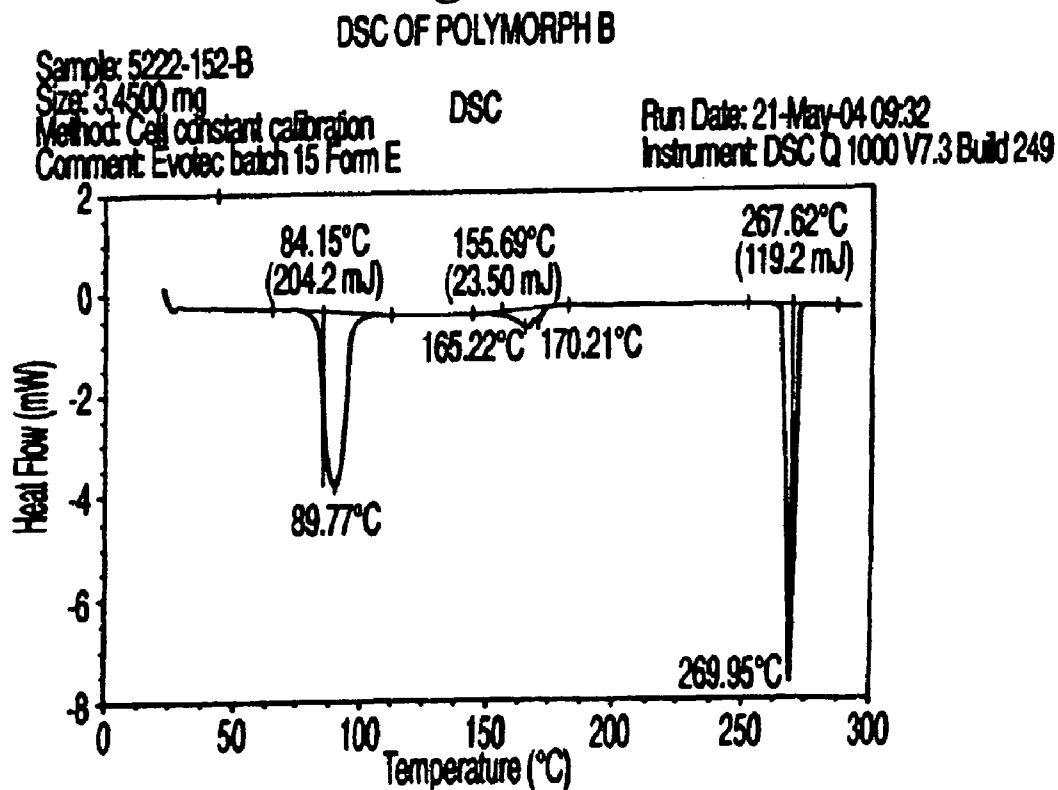
*Fig. 42**Fig. 43*

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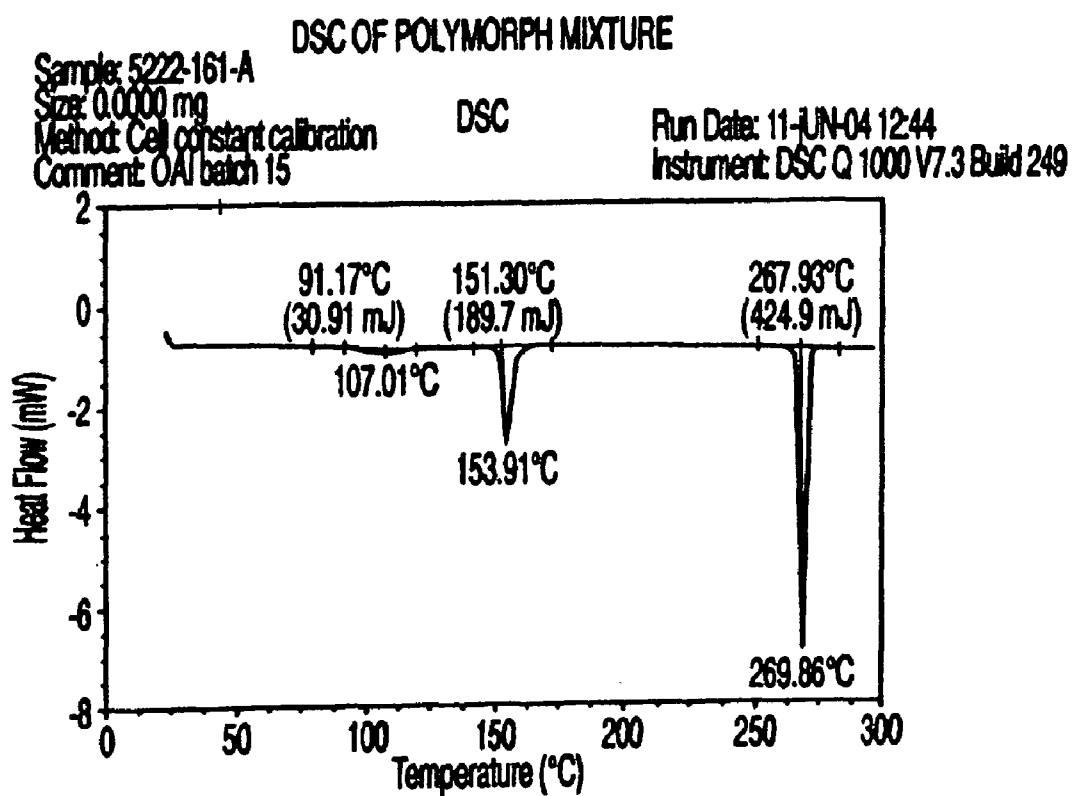
*Fig. 44**Fig. 45*

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*Fig. 46*

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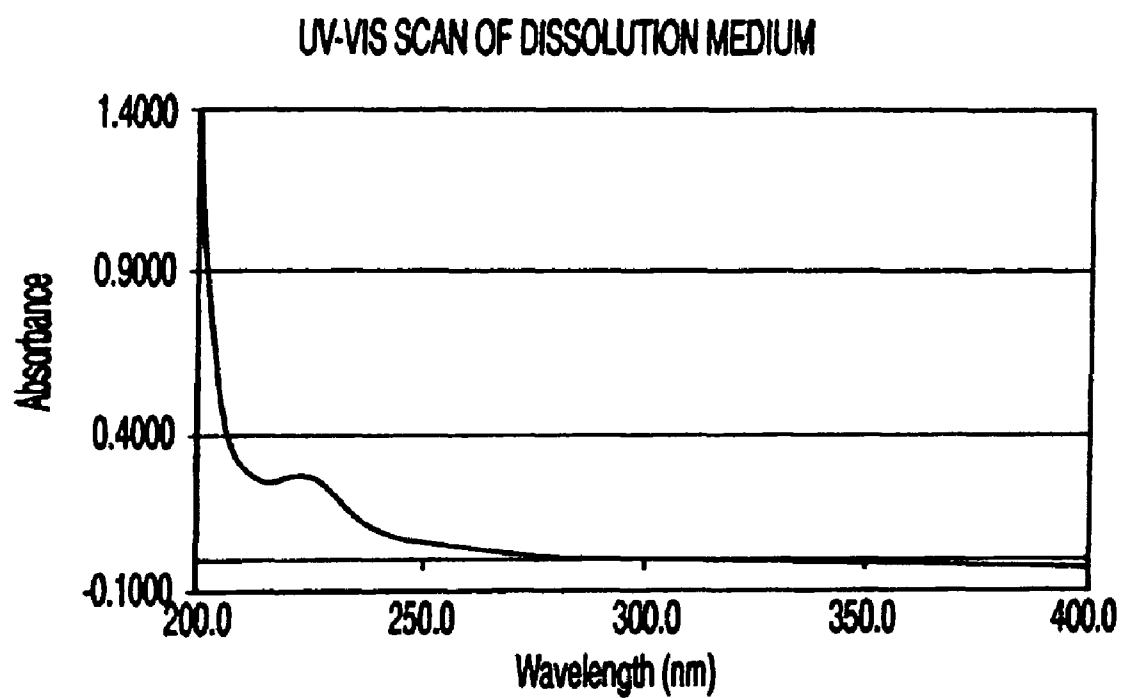


Fig. 47

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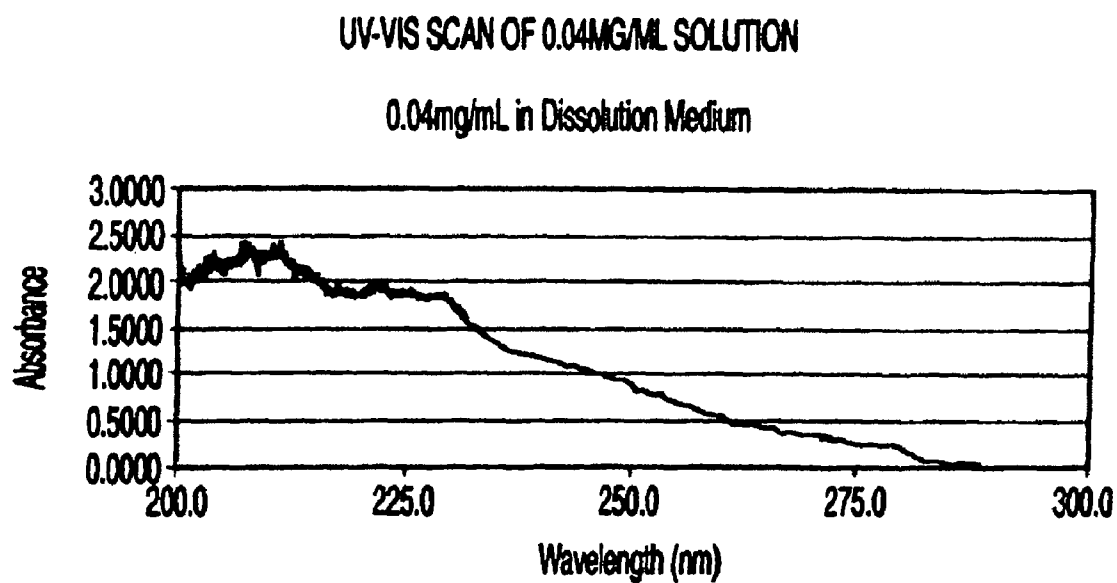


Fig. 48

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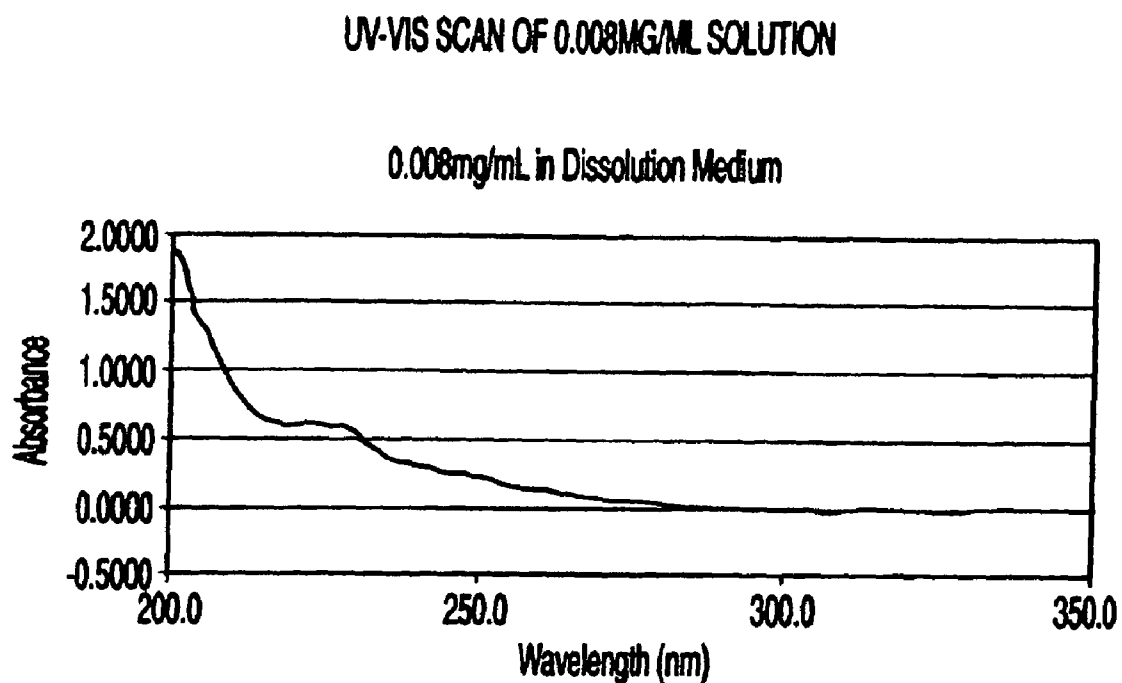
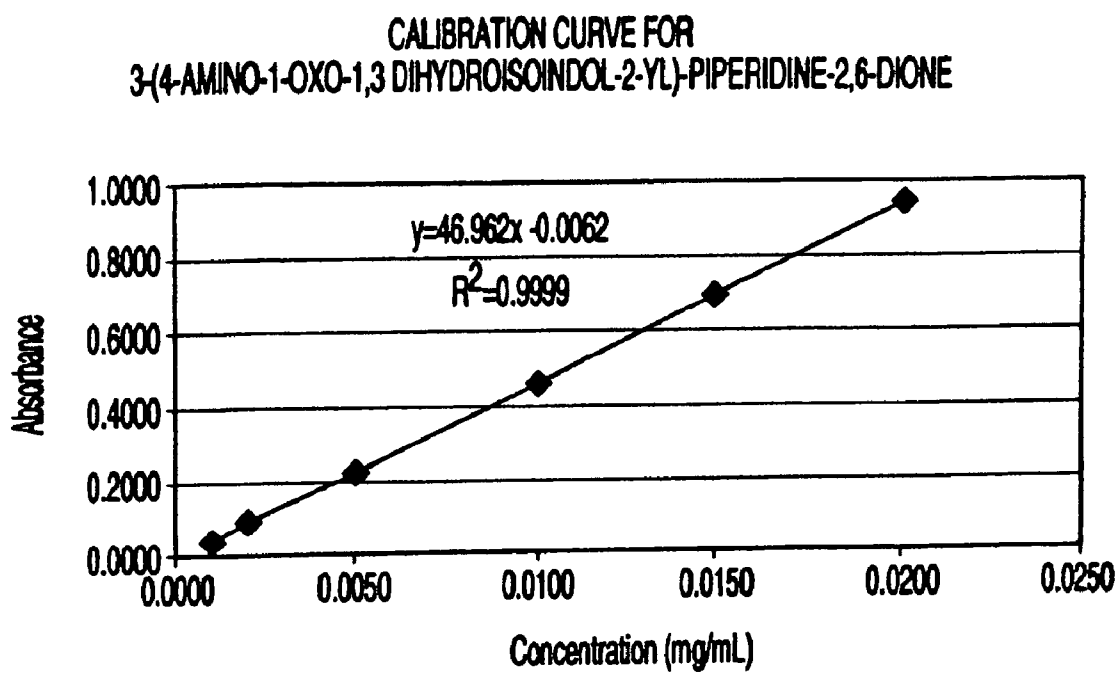


Fig. 49

*Fig. 50*

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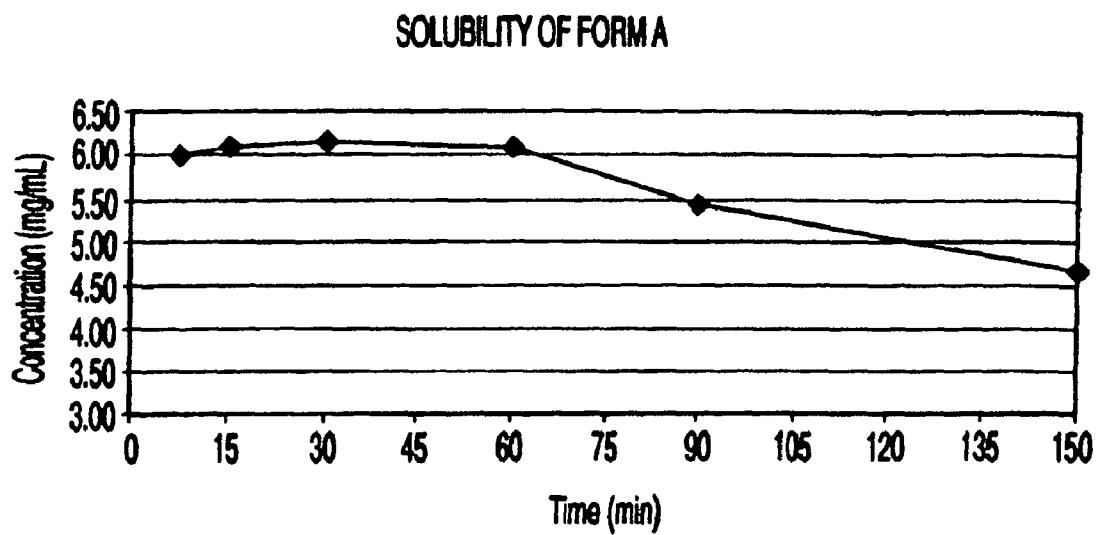


Fig. 51

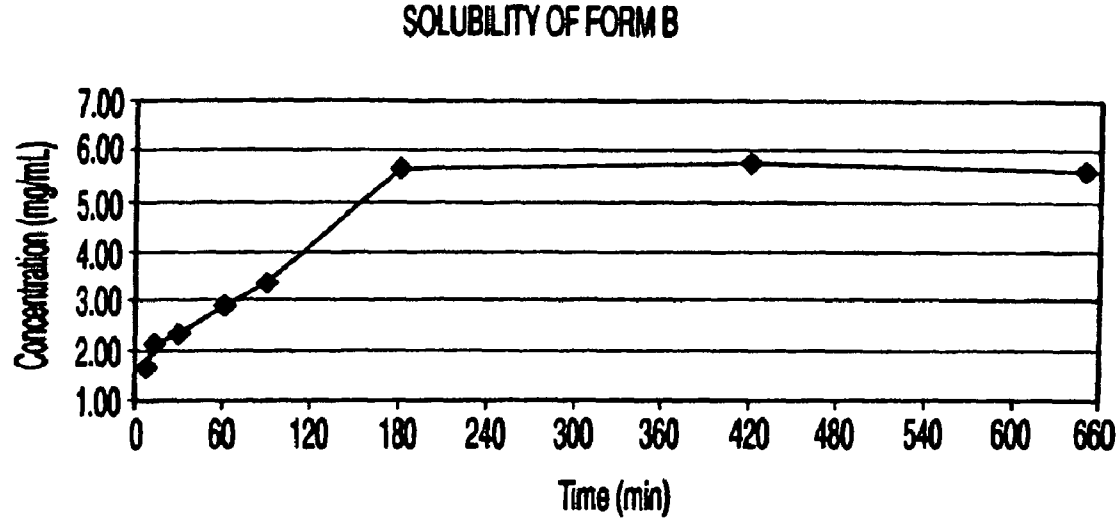


Fig. 52

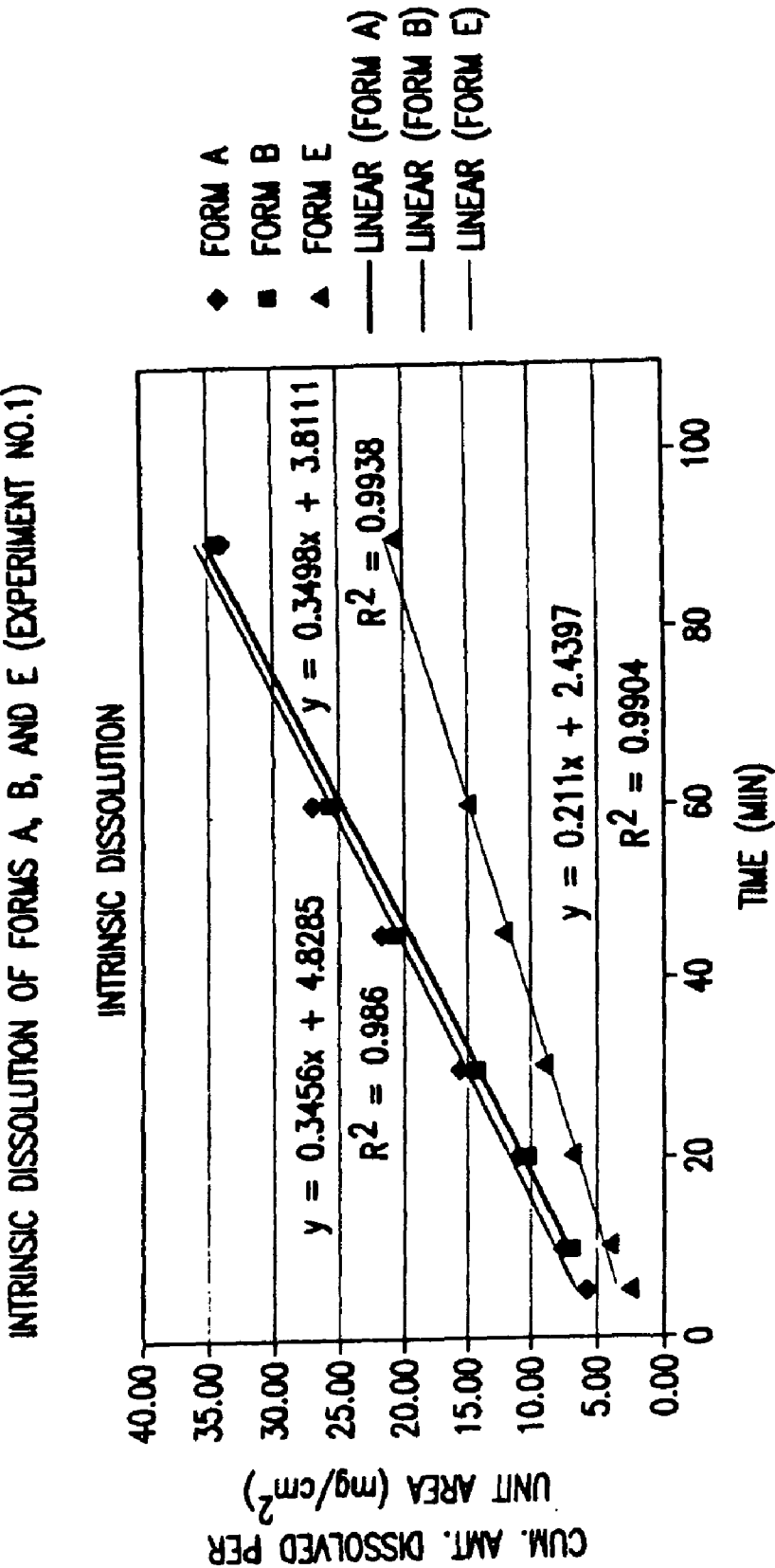


FIG.53

INTRINSIC DISSOLUTION OF FORMS A, B, AND E (EXPERIMENT NO.2)

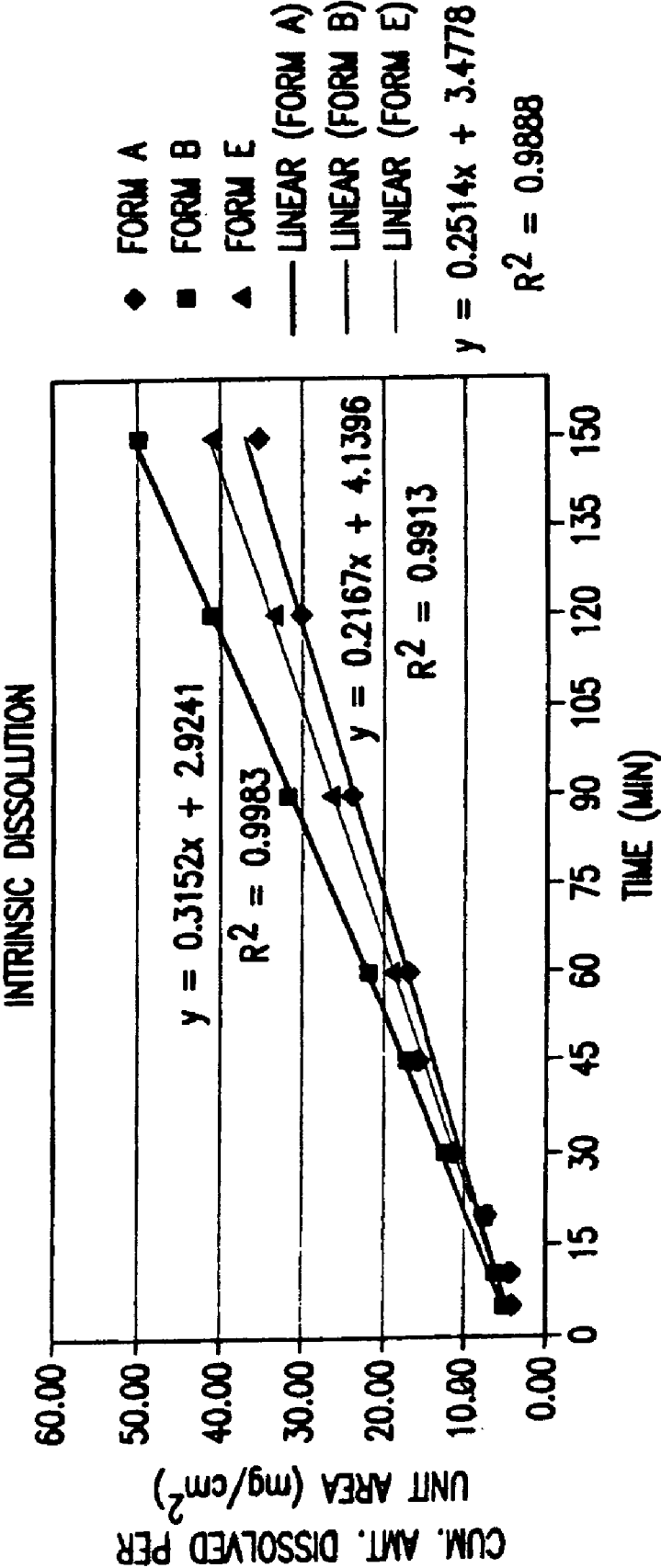


FIG.54

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**POLYMORPHIC FORMS OF
3-(4-AMINO-1-OXO-1,3
DIHYDRO-ISOINDOL-2-YL)-
PIPERIDINE-2,6-DIONE**

This application is a divisional application of U.S. patent application Ser. No. 10/934,863, filed Sep. 3, 2004, now U.S. Pat. No. 7,465,800 presently pending, which claims the benefit of U.S. provisional application 60/499,723, filed Sep. 4, 2003, the contents of each of which are incorporated by reference herein in their entireties.

1. FIELD OF THE INVENTION

This invention relates to polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione, compositions comprising the polymorphic forms, methods of making the polymorphic forms and methods of their use for the treatment of diseases and conditions including, but not limited to, inflammatory diseases, autoimmune diseases, and cancer.

2. BACKGROUND OF THE INVENTION

Many compounds can exist in different crystal forms, or polymorphs, which exhibit different physical, chemical, and spectroscopic properties. For example, certain polymorphs of a compound may be more readily soluble in particular solvents, may flow more readily, or may compress more easily than others. See, e.g., P. DiMartino, et al., *J. Thermal Anal.*, 48:447-458 (1997). In the case of drugs, certain solid forms may be more bioavailable than others, while others may be more stable under certain manufacturing, storage, and biological conditions. This is particularly important from a regulatory standpoint, since drugs are approved by agencies such as the U.S. Food and Drug Administration only if they meet exacting purity and characterization standards. Indeed, the regulatory approval of one polymorph of a compound, which exhibits certain solubility and physico-chemical (including spectroscopic) properties, typically does not imply the ready approval of other polymorphs of that same compound.

Polymorphic forms of a compound are known in the pharmaceutical arts to affect, for example, the solubility, stability, flowability, fractability, and compressibility of the compound, as well as the safety and efficacy of drug products comprising it. See, e.g., Knapman, K. *Modern Drug Discoveries*, 2000, 53. Therefore, the discovery of new polymorphs of a drug can provide a variety of advantages.

U.S. Pat. Nos. 5,635,517 and 6,281,230, both to Muller et al., disclose 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione, which is useful in treating and preventing a wide range of diseases and conditions including, but not limited to, inflammatory diseases, autoimmune diseases, and cancer. New polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione can further the development of formulations for the treatment of these chronic illnesses, and may yield numerous formulation, manufacturing and therapeutic benefits.

3. SUMMARY OF THE INVENTION

This invention encompasses polymorphs of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. In certain aspects, the invention provides polymorphs of the compound identified herein as forms A, B, C, D, E, F, G, and H. The invention also encompasses mixtures of these forms. In further embodiments, this invention provides methods of making, isolating and characterizing the polymorphs.

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This invention also provides pharmaceutical compositions and single unit dosage forms comprising a polymorph of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. The invention further provides methods for the treatment or prevention of a variety of diseases and disorders, which comprise administering to a patient in need of such treatment or prevention a therapeutically effective amount of a polymorph of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione.

4. BRIEF DESCRIPTION OF THE DRAWINGS

Specific aspects of the invention can be understood with reference to the attached figures:

FIG. 1 provides a representative X-ray powder diffraction (XRPD) pattern of Form A;

FIG. 2 provides a representative IR spectrum of Form A;

FIG. 3 provides a representative Raman spectrum of Form A;

FIG. 4 provides a representative thermogravimetric analysis (TGA) curve and a representative differential scanning calorimeter (DSC) thermogram of Form A;

FIG. 5 provides a representative moisture sorption/desorption isotherm of Form A;

FIG. 6 provides a representative XRPD pattern of Form B;

FIG. 7 provides a representative IR spectrum of Form B;

FIG. 8 provides a representative Raman spectrum of Form B;

FIG. 9 provides a representative TGA curve and a representative DSC thermogram of Form B;

FIG. 10 provides representative TG-IR results of Form B;

FIG. 11 provides a representative moisture sorption/desorption isotherm of Form B;

FIG. 12 provides a representative XRPD pattern of Form C;

FIG. 13 provides a representative IR spectrum of Form C;

FIG. 14 provides a representative Raman spectrum of Form C;

FIG. 15 provides a representative TGA curve and a representative DSC thermogram of Form C;

FIG. 16 provides representative TG-IR results of Form C;

FIG. 17 provides a representative moisture sorption/desorption isotherm of Form C;

FIG. 18 provides a representative XRPD pattern of Form D;

FIG. 19 provides a representative IR spectrum of Form D;

FIG. 20 provides a representative Raman spectrum of Form D;

FIG. 21 provides a representative TGA curve and a representative DSC thermogram of Form D;

FIG. 22 provides a representative moisture sorption/desorption isotherm of Form D;

FIG. 23 provides a representative XRPD pattern of Form E;

FIG. 24 provides a representative TGA curve and a representative DSC thermogram of Form E;

FIG. 25 provides a representative moisture sorption/desorption isotherm of Form E;

FIG. 26 provides a representative XRPD pattern for a sample of Form F;

FIG. 27 provides a representative thermogram of Form F;

FIG. 28 provides a representative XRPD pattern of Form G;

FIG. 29 provides a representative DSC thermogram for a sample of Form G;

FIG. 30 provides a representative XRPD pattern of Form H;

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FIG. 31 provides a representative TGA curve and a representative DSC thermogram of Form H;

FIG. 32 provides a representative XRPD pattern of Form B;

FIG. 33 provides a representative XRPD pattern of Form B;

FIG. 34 provides a representative XRPD pattern of Form B;

FIG. 35 provides a representative XRPD pattern of Form E;

FIG. 36 provides a representative XRPD pattern of polymorph mixture;

FIG. 37 provides a representative TGA curve of Form B;

FIG. 38 provides a representative TGA curve of Form B;

FIG. 39 provides a representative TGA curve of Form B;

FIG. 40 provides a representative TGA curve of Form E;

FIG. 41 provides a representative TGA curve of polymorph mixture;

FIG. 42 provides a representative DSC thermogram of Form B;

FIG. 43 provides a representative DSC thermogram of Form B;

FIG. 44 provides a representative DSC thermogram of Form B;

FIG. 45 provides a representative DSC thermogram of Form E;

FIG. 46 provides a representative DSC thermogram of polymorph mixture;

FIG. 47 provides a UV-Vis scan of dissolution medium;

FIG. 48 provides a UV-Vis scan of 0.04 mg/ml of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione in dissolution medium;

FIG. 49 provides a UV-Vis scan of 0.008 mg/ml of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione in dissolution medium;

FIG. 50 provides a calibration curve for 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione;

FIG. 51 provides a solubility curve of Form A;

FIG. 52 provides a solubility curve of Form B;

FIG. 53 provides an intrinsic dissolution of Forms A, B and E; and

FIG. 54 provides an intrinsic dissolution of Forms A, B and E.

5. DETAILED DESCRIPTION OF THE INVENTION

5.1 Definitions

As used herein and unless otherwise indicated, the terms “treat,” “treating” and “treatment” refer to the alleviation of a disease or disorder and/or at least one of its attendant symptoms.

As used herein and unless otherwise indicated, the terms “prevent,” “preventing” and “prevention” refer to the inhibition of a symptom of a disease or disorder or the disease itself.

As used herein and unless otherwise indicated, the terms “polymorph” and “polymorphic form” refer to solid crystalline forms of a compound or complex. Different polymorphs of the same compound can exhibit different physical, chemical and/or spectroscopic properties. Different physical properties include, but are not limited to stability (e.g., to heat or light), compressibility and density (important in formulation and product manufacturing), and dissolution rates (which can affect bioavailability). Differences in stability can result from changes in chemical reactivity (e.g., differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical characteristics (e.g., tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both

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(e.g., tablets of one polymorph are more susceptible to breakdown at high humidity). Different physical properties of polymorphs can affect their processing. For example, one polymorph might be more likely to form solvates or might be more difficult to filter or wash free of impurities than another due to, for example, the shape or size distribution of particles of it.

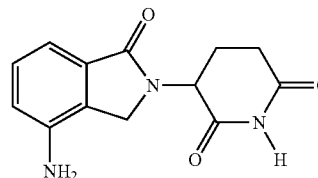
Polymorphs of a molecule can be obtained by a number of methods known in the art. Such methods include, but are not limited to, melt recrystallization, melt cooling, solvent recrystallization, desolvation, rapid evaporation, rapid cooling, slow cooling, vapor diffusion and sublimation. Polymorphs can be detected, identified, classified and characterized using well-known techniques such as, but not limited to, differential scanning calorimetry (DSC), thermogravimetry (TGA), X-ray powder diffractometry (XRPD), single crystal X-ray diffractometry, vibrational spectroscopy, solution calorimetry, solid state nuclear magnetic resonance (NMR), infrared (IR) spectroscopy, Raman spectroscopy, hot stage optical microscopy, scanning electron microscopy (SEM), electron crystallography and quantitative analysis, particle size analysis (PSA), surface area analysis, solubility, and rate of dissolution.

As used herein to refer to the spectra or data presented in graphical form (e.g., XRPD, IR, Raman and NMR spectra), and unless otherwise indicated, the term “peak” refers to a peak or other special feature that one skilled in the art would recognize as not attributable to background noise. The term “significant peaks” refers to peaks at least the median size (e.g., height) of other peaks in the spectrum or data, or at least 1.5, 2, or 2.5 times the median size of other peaks in the spectrum or data.

As used herein and unless otherwise indicated, the term “substantially pure” when used to describe a polymorph of a compound means a solid form of the compound that comprises that polymorph and is substantially free of other polymorphs of the compound. A representative substantially pure polymorph comprises greater than about 80% by weight of one polymorphic form of the compound and less than about 20% by weight of other polymorphic forms of the compound, more preferably greater than about 90% by weight of one polymorphic form of the compound and less than about 10% by weight of the other polymorphic forms of the compound, even more preferably greater than about 95% by weight of one polymorphic form of the compound and less than about 5% by weight of the other polymorphic forms of the compound, and most preferably greater than about 97% by weight of one polymorphic forms of the compound and less than about 3% by weight of the other polymorphic forms of the compound.

5.2 Polymorphic Forms

This invention is directed to polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione, which has the structure shown below:



This compound can be prepared according to the methods described in U.S. Pat. Nos. 6,281,230 and 5,635,517, the entireties of which are incorporated herein by reference. For

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example, the compound can be prepared through catalytic hydrogenation of 3-(4-nitro-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. 3-(4-Nitro-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione can be obtained by allowing 2,6-dioxopiperidin-3-ammonium chloride to react with methyl 2-bromomethyl-4-nitrobenzoate in dimethylformamide in the presence of triethylamine. The methyl 2-bromomethyl-4-nitrobenzoate in turn is obtained from the corresponding methyl ester of nitro-ortho-toluic acid by conventional bromination with N-bromosuccinimide under the influence of light.

Polymorphs of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione can be obtained by techniques known in the art, including solvent recrystallization, desolvation, vapor diffusion, rapid evaporation, slow evaporation, rapid cooling and slow cooling. Polymorphs can be made by dissolving a weighed quantity of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione in various solvents at elevated temperatures. The solutions of the compound can then be filtered and allowed to evaporate either in an open vial (for fast hot evaporation) or in a vial covered with aluminum foil containing pinholes (hot slow evaporation). Polymorphs can also be obtained from slurries. Polymorphs can be crystallized from solutions or slurries using several methods. For example, a solution created at an elevated temperature (e.g., 60° C.) can be filtered quickly then allowed to cool to room temperature. Once at room temperature, the sample that did not crystallize can be moved to a refrigerator then filtered. Alternatively, the solutions can be crash cooled by dissolving the solid in a solvent at an increased temperature (e.g., 45-65° C.) followed by cooling in a dry ice/solvent bath.

One embodiment of the invention encompasses Form A of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form A is an unsolvated, crystalline material that can be obtained from non-aqueous solvent systems. Another embodiment of the invention encompasses Form B of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form B is a hemihydrated, crystalline material that can be obtained from various solvent systems. Another embodiment of the invention encompasses Form C of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form C is a hemisolvated crystalline material that can be obtained from solvents such as, but not limited to, acetone. Another embodiment of the invention encompasses Form D of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form D is a crystalline, solvated polymorph prepared from a mixture of acetonitrile and water. Another embodiment of the invention encompasses Form E of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form E is a dihydrated, crystalline material. Another embodiment of the invention encompasses Form F of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form F is an unsolvated, crystalline material that can be obtained from the dehydration of Form E. Another embodiment of the invention encompasses Form G of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form G is an unsolvated, crystalline material that can be obtained from slurrying forms B and E in a solvent such as, but not limited to, tetrahydrofuran (THF). Another embodiment of the invention encompasses Form H of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Form H is a partially hydrated crystalline material that can be obtained by exposing Form E to 0% relative humidity. Each of these forms is discussed in detail below.

Another embodiment of the invention encompasses a composition comprising amorphous 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione and crystalline 3-(4-

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amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione of form A, B, C, D, E, F, G or H. Specific compositions can comprise greater than about 50, 75, 90 or 95 weight percent crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione.

Another embodiment of the invention encompasses a composition comprising at least two crystalline forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione (e.g., a mixture of polymorph forms B and E).

5.2.1 Form A

The data described herein for Form A, as well as for Forms B-H, were obtained using the experimental methods described in Examples 6.3-6.7, provided below.

Form A can be obtained from various solvents, including, but not limited to 1-butanol, butyl acetate, ethanol, ethyl acetate, methanol, methyl ethyl ketone, and THF. FIG. 1 shows a representative XRPD pattern of Form A. The pattern is characterized by peaks, preferably significant peaks, at approximately 8, 14.5, 16, 17.5, 20.5, 24, and 26 degrees 2θ. Representative IR and Raman spectra data are provided in FIGS. 2 and 3.

Representative thermal characteristics of Form A are shown in FIG. 4. TGA data show a small weight increase up to about 150° C., indicating an unsolvated material. Weight loss above 150° C. is attributed to decomposition. The DSC curve of Form A exhibits an endotherm at about 270° C.

Representative moisture sorption and desorption data are plotted in FIG. 5. Form A does not exhibit a significant weight gain from 5 to 95% relative humidity. Equilibrium can be obtained at each relative humidity step. As the form dries from 95% back down to 5% relative humidity, it tends to maintain its weight such that at 5% relative humidity it has typically lost only about 0.003% by weight from start to finish. Form A is capable of remaining a crystalline solid for about 11 days when stored at about 22, 45, 58, and 84% relative humidity.

Interconversion studies show that Form A can convert to Form B in aqueous solvent systems and can convert to Form C in acetone solvent systems. Form A tends to be stable in anhydrous solvent systems. In water systems and in the presence of Form E, Form A tends to convert to Form E.

When stored for a period of about 85 days under two different temperature/relative humidity stress conditions (room temperature/0% relative humidity (RH) and 40° C./93% RH), Form A typically does not convert to a different form.

In sum, Form A is a crystalline, unsolvated solid that melts at approximately 270° C. Form A is weakly or not hygroscopic and appears to be the most thermodynamically stable anhydrous polymorph of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione discovered thus far.

5.2.2 Form B

Form B can be obtained from many solvents, including, but not limited to, hexane, toluene, and water. FIG. 6 shows a representative XRPD pattern of Form B, characterized by peaks at approximately 16, 18, 22 and 27 degrees 2θ.

Solution proton NMR confirm that Form B is a form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Representative IR and Raman spectra are shown in FIGS. 7 and 8, respectively. Compared to Form A, the IR spectrum for Form B has peaks at approximately 3513 and 1960 cm⁻¹.

Representative DSC and TGA data for Form B are shown in FIG. 9. The DSC curve exhibits endotherms at about 146 and 268° C. These events are identified as dehydration and melting by hot stage microscopy experiments. Form B typically loses about 3.1% volatiles up to about 175° C. (per

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approximately 0.46 moles of water). Comparison of the IR spectrum of the volatiles with that of water indicates that they are water (See FIG. 10). Calculations from TGA data indicate that Form B is a hemihydrate. Karl Fischer water analysis also supports this conclusion.

Representative moisture sorption and desorption data are shown in FIG. 11. Form B typically does not exhibit a significant weight gain from 5% to 95% relative humidity, when equilibrium is obtained at each relative humidity step. As Form B dries from 95% back down to 5% relative humidity, it tends to maintain its weight such that at 5% relative humidity it typically has gained only about 0.022% by weight (about 0.003 mg) from start to finish. Form B does not convert to a different form upon exposure to about 84% relative humidity for about ten days.

Interconversion studies show that Form B typically converts to Form A in a THF solvent system, and typically converts to Form C in an acetone solvent system. In aqueous solvent systems such as pure water and 10% water solutions, Form B is the most stable of the polymorphic forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. However, it can convert to Form E in the presence of water. Desolvation experiments show that upon heating at about 175° C. for about five minutes, Form B typically converts to Form A.

When stored for a period of about 85 days under two different temperature/relative humidity stress conditions (room temperature/0% RH and 40° C./93% RH), Form B does not convert to a different form.

In sum, Form B is a hemihydrated, crystalline solid which has a DSC thermogram exhibiting endotherms at about 146 and about 268° C. Interconversion studies show that Form B converts to Form E in aqueous solvent systems, and converts to other forms in acetone and other anhydrous systems.

5.2.3 Form C

Form C can be obtained from evaporations, slurries and slow cools in acetone solvent systems. A representative XRPD pattern of this form is shown in FIG. 12. The data are characterized by peaks at approximately 15.5 and 25 degrees 2 θ .

Solution proton NMR indicates that the 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione molecule is intact. Representative IR and Raman spectra are shown in FIGS. 13 and 14, respectively. The IR spectrum of Form C is characterized by peaks at approximately 3466, 3373, and 3318 cm⁻¹. The Raman spectrum of Form C is characterized by peaks at about 3366, 3321, 1101, and 595 cm⁻¹.

Representative thermal characteristics for Form C are plotted in FIG. 15. Form C loses about 10.02% volatiles up to about 175° C., indicating it is a solvated material. Weight loss above about 175° C. is attributed to decomposition. Identification of volatiles in Form C can be accomplished with TG-IR experiments. The representative IR spectrum captured after several minutes of heating, as depicted in FIG. 13, when compared with a spectral library, shows acetone to be the best match. Calculations from TGA data show that Form C is a hemisolvate (approximately 0.497 moles of acetone). The DSC curve for Form C, shown in FIG. 15, exhibits endotherms at about 150 and about 269° C. The endotherm at about 150° C. is attributed to solvent loss based on observations made during hot stage microscopy experiments. The endotherm at about 269° C. is attributed to the melt based on hot stage experiments.

Representative moisture sorption and desorption balance data are shown in FIG. 17. Form C does not exhibit a significant weight gain from 5 to 85% relative humidity, when equilibrium is obtained at each relative humidity step up to

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85% relative humidity. At 95% relative humidity, Form C experiences a significant weight loss of about 6.03%. As the sample dries from 95% back down to 5% relative humidity, the sample maintains the weight achieved at the end of the adsorption phase at each step down to 5% relative humidity. Form C is capable of converting to Form B when stored at about 84% relative humidity for approximately ten days.

Interconversion studies show that Form C typically converts to Form A in a THF solvent system and typically converts to Form E in an aqueous solvent system. In an acetone solvent system, Form C is the most stable form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Desolvation experiments performed on Form C show that upon heating at about 150° C. for about five minutes, Form C will typically convert to Form A.

In sum, Form C is a crystalline, hemisolvated solid, which has a DSC thermogram exhibiting endotherms at about 150 and about 269° C. Form C is not hygroscopic below about 85% RH, but can convert to Form B at higher relative humidities.

5.2.4 Form D

Form D can be obtained from evaporation in acetonitrile solvent systems. A representative XRPD pattern of the form is shown in FIG. 18. The pattern is characterized by peaks at approximately 27 and 28 degrees 2 θ .

Solution proton NMR indicates that the 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione molecule is intact. Representative IR and Raman spectra are shown in FIGS. 19 and 20, respectively. The IR spectrum of Form D is characterized by peaks at approximately 3509, 2299, and 2256 cm⁻¹. The Raman spectrum of Form D is characterized by peaks at approximately 2943, 2889, 2297, 2260, 1646, and 1150 cm⁻¹.

Representative thermal characteristics for Form D are plotted in FIG. 21. Form D loses about 6.75% volatiles up to about 175° C., indicating a solvated material. Weight loss above about 175° C. is attributed to decomposition. TG-IR experiments indicate that the volatiles are water and acetonitrile. Calculations from TG data show that about one mole of water is present in the sample. A representative DSC curve for Form D exhibits endotherms at about 122 and about 270° C. The endotherm at about 122° C. is attributed to loss of volatiles based on observations made during hot stage microscopy experiments. The endotherm at about 270° C. is attributed to the melt based on hot stage experiments.

Representative moisture sorption and desorption data are plotted in FIG. 22. Form D does not exhibit a significant weight gain from 5 to 95% relative humidity when equilibrium is obtained at each relative humidity step. As the form dries from 95% back down to 5% relative humidity, it maintains its weight such that at 5% relative humidity the form has typically gained only about 0.39% by weight (about 0.012 mg) from start to finish. Form A is capable of converting to Form B when stored at about 84% relative humidity for approximately ten days.

Interconversion studies show that Form D is capable of converting to Form A in a THF solvent system, to Form E in an aqueous solvent system, and to Form C in an acetone solvent system. Desolvation experiments performed on Form D show that upon heating at about 150° C. for about five minutes Form D will typically convert to Form A.

In sum, Form D is a crystalline solid, solvated with both water and acetonitrile, which has a DSC thermogram exhibiting endotherms at about 122 and about 270° C. Form D is either weakly or not hygroscopic, but will typically convert to Form B when stressed at higher relative humidities.

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5.2.5 Form E

Form E can be obtained by slurrying 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione in water and by a slow evaporation of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione in a solvent system with a ratio of about 9:1 acetone:water. A representative XRPD pattern is shown in FIG. 23. The data are characterized by peaks at approximately 20, 24.5 and 29 degrees 2 θ .

Representative thermal characteristics of Form E are plotted in FIG. 24. Form E typically loses about 10.58% volatiles up to about 125° C., indicating that it is a solvated material. A second weight loss of an additional about 1.38% was observed between about 125° C. and about 175° C. Weight loss above about 175° C. is attributed to decomposition. Karl Fischer and TG-IR experiments support the conclusion that the volatile weight loss in Form E is due to water. The representative DSC curve for Form E exhibits endotherms at about 99, 161 and 269° C. Based on observations made during hot stage microscopy experiments, the endotherms at about 99 and about 161° C. are attributed to loss of volatiles. The endotherm at about 269° C. is attributed to the melt based on hot stage experiments.

Representative moisture sorption and desorption data are plotted in FIG. 25. Form E typically does not exhibit a significant weight change from 5 to 95% relative humidity when equilibrium is obtained at each relative humidity step. As the sample dried from 95% back down to 5% relative humidity, the sample continues to maintain weight such that at 5% relative humidity the sample has lost only about 0.0528% by weight from start to finish.

Interconversion studies show that Form E can convert to Form C in an acetone solvent system and to Form G in a THF solvent system. In aqueous solvent systems, Form E appears to be the most stable form. Desolvation experiments performed on Form E show that upon heating at about 125° C. for about five minutes, Form E can convert to Form B. Upon heating at 175° C. for about five minutes, Form B can convert to Form F.

When stored for a period of 85 days under two different temperature/relative humidity stress conditions (room temperature/0% RH and 40° C./93% RH) Form E typically does not convert to a different form. When stored for seven days at room temperature/0% RH, Form E can convert to a new form, Form H.

5.2.6 Form F

Form F can be obtained by complete dehydration of Form E. A representative XRPD pattern of Form F, shown in FIG. 26, is characterized by peaks at approximately 19, 19.5 and 25 degrees 2 θ .

Representative thermal characteristics of Form F are shown in FIG. 27. The representative DSC curve for Form F exhibits an endotherm at about 269° C. preceded directly by two smaller endotherms indicative of a crystallized form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. The DSC thermogram does not show any thermal events prior to the melt, suggesting that it is an unsolvated material.

5.2.7 Form G

Form G can be obtained by slurrying forms B and E in THF. A representative XRPD pattern of this form, shown in FIG. 28, is characterized by a peak at approximately 23 degrees 2 θ . Two other peaks unique to Form G appear at approximately 21 and 24.5 degrees 2 θ .

Representative thermal characteristics of Form G are plotted in FIG. 29. A representative DSC curve for Form G exhibits an endotherm at about 248° C. followed by a small, broad exotherm at about 267° C. No thermal events are seen

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in the DSC thermogram at lower temperatures, suggesting that it is an unsolvated material.

5.2.8 Form H

Form H can be obtained by storing Form E at room temperature and 0% RH for about 7 days. A representative XRPD pattern is shown in FIG. 30. The pattern is characterized by a peak at 15 degrees 2 θ , and two other peaks at 26 and 31 degrees 2 θ .

Representative thermal characteristics are shown in FIG. 31. Form H loses about 1.67% volatiles up to about 150° C. Weight loss above about 150° C. is attributed to decomposition. Karl Fischer data shows that Form H typically contains about 1.77% water (about 0.26 moles), suggesting that the weight loss seen in the TG is due to dehydration. The DSC thermogram shows a broad endotherm between about 50° C. and about 125° C., corresponding to the dehydration of Form H and a sharp endotherm at about 269° C., which is likely due to a melt.

When slurried in water with either Forms A or B, after about 14 days Form H can convert to Form E. When slurried in THF, Form H can convert to Form A. When slurried in acetone, Form H can convert to Form C.

In sum, Form H is a crystalline solid, hydrated with about 0.25 moles of water, which has a DSC thermogram exhibiting an endotherm between about 50 and 125° C. and an endotherm at about 269° C.

5.3 Methods of Use and Pharmaceutical Compositions

Polymorphs of the invention exhibit physical characteristics that are beneficial for drug manufacture, storage or use. All polymorphs of the invention have utility as pharmaceutically active ingredients or intermediates thereof.

This invention encompasses methods of treating and preventing a wide variety of diseases and conditions using polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. In each of the methods, a therapeutically or prophylactically effective amount of the compound is administered to a patient in need of such treatment or prevention. Examples of such disease and conditions include, but are not limited to, diseases associated with undesired angiogenesis, cancer (e.g., solid and blood borne tumors), inflammatory diseases, autoimmune diseases, and immune diseases. Examples of cancers and pre-cancerous conditions include those described in U.S. Pat. Nos. 6,281,230 and 5,635,517 to Muller et al. and in various U.S. patent applications to Zeldis, including application Ser. Nos. 10/411,649, filed Apr. 11, 2003 (Treatment of Myelodysplastic Syndrome); 10/438,213 filed May 15, 2003 (Treatment of Various Types of Cancer); 10/411,656, filed Apr. 11, 2003 (Treatment of Myeloproliferative Diseases). Examples of other diseases and disorders that can be treated or prevented using compositions of the invention are described in U.S. Pat. Nos. 6,235,756 and 6,114,335 to D'Amato and in other U.S. patent applications to Zeldis, including Ser. Nos. 10/693,794, filed Oct. 23, 2003 (Treatment of Pain Syndrome) and 10/699,154, filed Oct. 30, 2003 (Treatment of Macular Degeneration). The entirety of each of the patents and patent applications cited herein is incorporated herein by reference.

Depending on the disease to be treated and the subject's condition, polymorphs of the invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implantation), inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit

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formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. Because individual polymorphs have different dissolution, stability, and other properties, the optimal polymorph used in methods of treatment may depend on the route of administration. For example, forms that are readily soluble in aqueous solutions are preferably used to provide liquid dosage forms, whereas forms that exhibit great thermal stability may be preferred in the manufacture of solid dosage forms (e.g., tablets and capsules).

Although the physical characteristics of polymorphs can, in some cases, affect their bioavailability, amounts of the polymorphs that are therapeutically or prophylactically effective in the treatment of various disease and conditions can be readily determined by those of ordinary skill in the pharmacy or medical arts. In certain embodiments of the invention, a polymorph is administered orally and in a single or divided daily doses in an amount of from about 0.10 to about 150 mg/day, or from about 5 to about 25 mg/day. In other embodiments, a polymorph is administered every other day in an amount of from about 0.10 to about 150 mg/day, or from about 5 to about 25 mg/day.

The invention encompasses pharmaceutical compositions and single unit dosage forms that can be used in methods of treatment and prevention, which comprise one or more polymorphs of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and optionally one or more excipients or diluents. Specific compositions and dosage forms are disclosed in the various patents and patent applications incorporated herein by reference. In one embodiment, a single dosage form comprises a polymorph (e.g., Form B) in an amount of about 5, 10, 25 or 50 mg.

6. EXAMPLES

6.1 Polymorph Screen

A polymorph screen to generate the different solid forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2, 6-dione was carried out as follows.

A weighed sample of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione (usually about 10 mg) was treated with aliquots of the test solvent. Solvents were either reagent or HPLC grade. The aliquots were usually about 200 μ L. Between additions, the mixture was usually shaken or sonicated. When the solids dissolved, as judged by visual inspection, estimated solubilities were calculated. Solubilities were estimated from these experiments based on the total solvent used to provide a solution. Actual solubilities may have been greater than those calculated due to the use of too-large solvent aliquots or to a slow rate of dissolution.

Samples were created by generating solutions (usually about 30 mg in 20 mL) at elevated temperatures, filtering, and allowing the solution to evaporate whether in an open vial (hot fast evaporation) or in a vial covered with aluminum foil containing pinholes (hot slow evaporation).

Slurry experiments were also performed. Usually about 25 mg of solid was placed in either 3 or 5 mL of solvent. The samples were then placed on orbital shakers at either ambient temperature or 40° C. for 410 days.

Crystallizations were performed using various cooling methods. Solid was dissolved in a solvent at an elevated temperature (e.g., about 60° C.), filtered quickly and allowed to cool to room temperature. Once at room temperature, samples that did not crystallize were moved to a refrigerator. Solids were removed by filtration or decantation and allowed

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to dry in the air. Crash cools were performed by dissolving solid in a solvent at an increased temperature (e.g., about 45-65° C.) followed by cooling in a dry ice/acetone bath.

Hygroscopicity studies were performed by placing portions of each polymorph in an 84% relative humidity chamber for approximately one week.

Desolvation studies were carried out by heating each polymorph in a 70° C. oven for approximately one week.

Interconversion experiments were carried out by making slurries containing two forms in a saturated solvent. The slurries were agitated for approximately 7-20 days at ambient temperature. The insoluble solids were recovered by filtration and analyzed using XRPD.

6.2 Preparation of Polymorphic Forms

Eight solid forms of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione were prepared as described below.

Form A was obtained by crystallization from various non-aqueous solvents including 1-butanol, butyl acetate, ethanol, ethyl acetate, methanol, methyl ethyl ketone, and tetrahydrofuran. Form B was also obtained by crystallization from the solvents hexane, toluene and water. Form C was obtained from evaporations, slurries, and slow cools in acetone solvent systems. Form D was obtained from evaporations in acetonitrile solvent systems. Form E was obtained most readily by slurrying 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione in water. Form F was obtained by complete desolvation of Form E. It is found to be an unsolvated, crystalline material that melts at about 269° C. Form G was obtained by slurrying forms B and E in THF. Form H was obtained by stressing Form E at room temperature and 0% RH for 7 days.

6.2.1 Synthesis of Polymorphs B and E

Form B is the desired polymorph for the active pharmaceutical ingredient (API) of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. This form has been used in the formulation of API into drug product for clinical studies. Three batches were produced as apparent mixtures of polymorphs in the non-micronized API of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione.

Development work was carried out to define a process that would generate polymorph B from this mixture of polymorphs and could be implemented for strict polymorphic controls in the validation batches and future manufacturing of API of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Characterization of polymorphic forms produced during the work was performed by XRPD, DSC, TGA and KF.

A process was also developed for the large-scale preparation of Form E. Polymorph E material was prepared in order to carry out a comparison with polymorph B drug product in capsule dissolution testing of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. 150 g of a mixture of polymorphs in 3 L of water was stirred at room temperature for 48 hours. The product was collected by filtration and dried at 25° C. for 24 hours under vacuum. XRPD, DSC, TGA, KF and HPLC analyses confirmed that the material isolated was polymorph E.

In a preliminary work, it was demonstrated that stirring a suspension of a mixture of polymorphs of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione with water at high temperature (75° C.) for an extended period of time converted this mixture of polymorphs exclusively to form B. Several specific parameters were identified including temperature, solvent volume and drying parameters (temperature

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and vacuum). XRPD, DSC, TGA, KF and HPLC analyses were used to characterize all of the batches. After completing the optimization work, the optimized process was scaled-up to 100-200 g on three lots of API. Drying studies were carried out at 20° C., 30° C. and 40° C., and 65° C. with a vacuum of 150 mm of Hg. The results are shown in Tables 1-5.

The cooling and holding periods of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione slurry were studied. The experimental laboratory data suggests that polymorph B seems to be forming first, and overtime equilibration to polymorph E at RT conditions occurs, therefore generating a mixture of polymorphs B and E. This result supports the fact that polymorph B seems to be a kinetic product, and that prolonged processing time converts the material to polymorph E resulting in a mixture of polymorphs B and E.

A laboratory procedure was developed to exclusively produce polymorph B of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. The procedure includes a stirred 10 volume water slurry at ~75° C. for 6-24 hours. The following preferred process parameters have been identified:

1. Hot slurry temperature of 70-75° C.
2. Product filtration of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)piperidine-2,6-dione at 65-75° C.
3. Drying under vacuum at 60-70° C. is preferred for an efficient removal of unbound water in 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione wet cake.
4. The filtration step of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione may be a time sensitive operation. The use of efficient solid-liquid separation equipment is preferred.
5. Holding periods of water-wet cake of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione at KF higher than 5% may cause the kinetic equilibrations of polymorph B to mixed polymorphs of E and B.

Drying to KF<4.0% water was achieved in ~3 hours (30-70° C., 152 mm Hg). Polymorphs B and E were distinguished by the water levels as measured by KF and TGA. The reference sample of polymorph B is micronized API. In order to make accurate comparison by XRPD samples were gently grinded before submission for analysis. This increases the clarity of the identification of the polymorphic form. All samples were analyzed for XRPD, DSC, TGA, KF and HPLC.

TABLE 1

Preliminary Studies			
Amount	Reaction conditions	Analysis	Results/conclusion
2 g	Water, rt, 48 h	XRPD, DSC, TGA, KF	Polymorph E
25 g	Water, rt, 48 h	XRPD, DSC, TGA, KF	Polymorph E
5 g	Water, 70-75° C., 24 h then rt 24 h	XRPD, DSC, TGA, KF	Polymorph B
1 g	9:1 Acetone - water, Slow evpo.	XRPD, DSC, TGA, KF	Polymorph Mixture
1 g	175° C. 1 h in an oven	XRPD, DSC, TGA, KF	Polymorph A
0.5 g (polymorph A)	Water, rt, 24 h	XRPD, DSC, TGA, KF	Polymorph E
1 g polymorph B	Water, rt, 48 h	XRPD, DSC, TGA, KF	Polymorph E
1 g polymorph E	Water, 70-75° C., 24 h	XRPD, DSC, TGA, KF	Polymorph B
1 g	Slurry in heptane	XRPD, DSC, TGA, KF	No change

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TABLE 2

Optimization of Temperature, Time and Solvent Volume				
Amount	Amount Water (mL)	Temp (° C.)	Time (h)	Results/conclusion
10 g	50	75	6	Mix
10 g	50	75	24	Polymorph B
10 g	100	70	6	Polymorph B
10 g	100	70	14	Polymorph B
10 g	100	70	21	Polymorph B
10 g	100	75	6	Polymorph B
10 g	100	75	24	Polymorph B
10 g	100	75	6	Polymorph B
10 g	100	75	19	Polymorph B
10 g	100	75	14	Polymorph B
10 g	100	75	24	Polymorph B
5 g	100	75	18	Polymorph B
10 g	100	80	6	Polymorph B
10 g	100	80	20	Polymorph B
10 g	200	45	6	Polymorph B + E
10 g	200	45	24	Polymorph E
10 g	200	60	48	Polymorph B
10 g	200	75	6	Mix
10 g	200	75	24	Polymorph B
10 g	200	75	13	Polymorph B
10 g	200	75	24	Polymorph B

Optimum conditions were determined to be 10 volumes of solvent (H₂O), 70-80° C. for 6-24 hours.

TABLE 3

Holding Time				
Amount	Reaction Conditions	Holding Time (h)	Holding Temp (° C.)	Results/Conclusion
5 g	Water, 70-75° C., 24 h	24	23-25	Polymorph B
1 g	Water, 70-75° C., 24 h	48	23-25	Polymorph E
Polymorph B				
2 g	Water, 40 mL	16	23-25	Polymorph E
150 g	Water, 3.0 L	24	23-25	Polymorph E
150 g	Water, 3.0 L	48	23-25	Polymorph E
10 g	Water, 100 mL, 24 h, 75° C.	18	23-25	Polymorph B
10 g	Water, 100 mL, 24 h, 75° C.	18	40	Polymorph B
10 g	Water, 200 mL, 24 h, 75° C.	14	-5	Mix
10 g	Water, 200 mL, 24 h, 75° C.	14	23-25	Polymorph E
10 g	Water, 200 mL, 24 h, 75° C.	14	40	Mix
10 g	Water, 100 mL, 24 h, 75° C.	21	23-25	Polymorph E
10 g	Water, 100 mL, 24 h, 75° C.	21	40	Mix
10 g	Water, 100 mL, 14 h, 75° C.	2	23-25	Mix

Holding time gave mixed results and it was determined that the material should be filtered at 60-65° C. and the material washed with 0.5 volume of warm (50-60° C.) water.

TABLE 4

Scale-up Experiments				
Amount	Amount Water (L)	Temp (° C.)	Time (h)	Results/Conclusion
100 g	1.0	75	6	Polymorph B
100 g	1.0	75	22	Polymorph B

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TABLE 4-continued

Scale-up Experiments				
Amount	Amount Water (L)	Temp (° C.)	Time (h)	Results/Conclusion
100 g	1.0	75	6	Polymorph B
100 g	1.0	75	24	Polymorph B
100 g	1.0	75	6	Polymorph B
100 g	1.0	75	22	Polymorph B

TABLE 5

Drying Studies					
Amount	Drying Time (h)	Drying Temp (° C.)	Vacuum (mm Hg)	KF§ (%)	Results/Conclusion
100 g	0	—	—	3.690	Polymorph B
100 g	3	30	152	3.452	Polymorph B
100 g	8	30	152	3.599	Polymorph B
100 g	0	—	—	3.917	Polymorph B
100 g	5	40	152	3.482	Polymorph B
100 g	22	40	152	3.516	Polymorph B
100 g	3	40	152	3.67	Polymorph B
100 g	22	40	152	3.55	Polymorph B

*Reaction Conditions: Water 1 L, 75° C., 22-24 h;

§Average of 2 runs.

Drying studies determined that the material should be dried at 35-40° C., 125-152 mm Hg for 3 to 22 h or until the water content reaches $\leq 4\%$ w/w.

For a large scale preparation of polymorph E (5222-152-B), a 5-L round bottom flask was charged with 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione (150 g, 0.579 mol) and water (3000 mL, 20 vol). The mixture was mechanically stirred at room temperature (23-25° C.) for 48 h under nitrogen atmosphere.

Samples were taken after 24 h and 48 h before the mixture was filtered and air-dried on the filter for 1 h. The material was transferred to a drying tray and dried at room temperature (23-25° C.) for 24 h. KF analysis on the dried material showed water content of 11.9%. The material was submitted for XRPD, TGA, DSC and HPLC analysis. Analysis showed the material was pure polymorph E.

For a large scale preparation of polymorph B (5274-104), a 2 L-3-necked round bottom flask was charged with 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione (polymorph mixture, 100 g, 0.386 mol) and water (1000 mL, 10.0 vol). The mixture was heated to 75° C. over approximately 30 minutes with mechanical stirring under nitrogen atmosphere.

Samples were taken after 6 h and 24 h before the mixture was allowed to cool to 60-65° C., filtered and the material washed with warm (50-60° C.) water (50 mL, 0.5 vol). The material was transferred to a drying tray and dried at 30° C., 152 mm Hg for 8 h. KF analysis on the dried material showed water content of 3.6%. After grinding the material was submitted for XRPD, TGA, DSC and HPLC analysis. Analysis showed the material was pure polymorph B. The results of the analyses are shown in FIGS. 32-46.

6.3 X-Ray Powder Diffraction Measurements

X-ray powder diffraction analyses were carried out on a Shimadzu XRD 6000 X-ray powder diffractometer using Cu K α radiation. The instrument is equipped with a fine-focus X-ray tube. The tube voltage and amperage were set at 40 kV

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and 40 mA, respectively. The divergence and scattering slits were set at 1° and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. A theta-two theta continuous scan at 3°/min (0.4 sec/0.02° step) from 2.5 degrees 2 θ to 40 degrees 2 θ was used. A silicon standard was analyzed each day to check the instrument alignment.

X-ray powder diffraction analyses were also carried out using Cu K α radiation on an Inel XRG-3000 diffractometer equipped with a curved position-sensitive detector. Data were collected in real time over a theta-two theta range of 120° at a resolution of 0.03°. The tube voltage and current were 40 kV and 30 mA, respectively. A silicon standard was analyzed each day to check for instrument alignment. Only the region between 2.5 and 40 degrees 2 θ is shown in the figures.

6.4 Thermal Analysis

TG analyses were carried out on a TA Instrument TGA 2050 or 2950. The calibration standards were nickel and alumel. Approximately 5 mg of sample was placed on a pan, accurately weighed, and inserted into the TG furnace. The samples were heated in nitrogen at a rate of 10° C./min, up to a final temperature of 300 or 350° C.

DSC data were obtained on a TA 2920 instrument. The calibration standard was indium. Approximately 2-5 mg samples were placed into a DSC pan and the weight accurately recorded. Crimped pans with one pinhole were used for analysis and the samples were heated under nitrogen at a rate of 10° C./min, up to a final temperature of 350° C.

Hot-stage microscopy was carried out using a Kofler hot stage mounted on a Leica Microscope. The instrument was calibrated using USP standards.

A TA Instruments TGA 2050 interfaced with a Nicolet model 560 Fourier transform IR spectrophotometer, equipped with a globar source, XT/KBr beamsplitter, and deuterated triglycine sulfate (DTGS) detector, was utilized for TG-IR experiments. The IR spectrometer was wavelength calibrated with polystyrene on the day of use while the TG was temperature and weight calibrated biweekly, using indium for the temperature calibration. A sample of approximately 10 mg of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione was weighed into an aluminum pan and heated from 25 to 30° C. to 200° C. at a rate of 20° C./min with a helium purge. IR spectra were obtained in series, with each spectrum representing 32 co-added scans at a resolution of 4 cm⁻¹. Spectra were collected with a 17-second repeat time. TG/IR analysis data are presented as Gram-Schmidt plots and IR spectra linked to the time. Gram-Schmidt plots show total IR intensity vs. time; hence, the volatiles can be identified at each time point. They also show when the volatiles are detected. From the Gram-Schmidt plots, time points were selected and the IR spectra of these time points are presented in the stacked linked spectra. Each spectrum identifies volatiles evolving at that time point. Volatiles were identified from a search of the HR Nicolet TGA vapor phase spectral library. The library match results are also presented to show the identified vapor.

6.5 Spectroscopy Measurements

Raman spectra were acquired on a Nicolet model 750 Fourier transform Raman spectrometer utilizing an excitation wavelength of 1064 nm and approximately 0.5 W of Nd:YAG laser power. The spectra represent 128 to 256 co-added scans acquired at 4 cm⁻¹ resolution. The samples were prepared for analysis by placing the material in a sample holder and posi-

tioning this in the spectrometer. The spectrometer was wavelength calibrated using sulfur and cyclohexane at the time of use.

The mid-IR spectra were acquired on a Nicolet model 860 Fourier transform IR spectrophotometer equipped with a global source XT/KBr beamsplitter and a deuterated triglycine sulfate (DTGS) detector. A Spectra-Tech, Inc. diffuse reflectance accessory was utilized for sampling. Each spectrum represents 128 co-added scans at a spectral resolution of 4 cm^{-1} . A background data set was acquired with an alignment mirror in place. A single beam sample data set was then acquired. Subsequently, a log 1/R (where R=reflectance) spectrum was acquired by rationing the two data sets against each other. The spectrophotometer was calibrated (wavelength) with polystyrene at the time of use.

6.6 Moisture Sorption/Desorption Measurements

Moisture sorption/desorption data were collected on a VTI SGA-100 moisture balance system. For sorption isotherms, a sorption range of 5 to 95% relative humidity (RH) and a desorption range of 95 to 5% RH in 10% RH increments was used for analysis. The sample was not dried prior to analysis. Equilibrium criteria used for analysis were less than 0.0100 weight percent change in 5 minutes with a maximum equilibration time of 3 hours if the weight criterion was not met. Data were not corrected for the initial moisture content of the samples.

6.7 Solution Proton NMR Measurements

NMR spectra not previously reported were collected at SSCI, Inc, 3065 Kent Avenue, West Lafayette, Ind. Solution phase ^1H NMR spectra were acquired at ambient temperature on a Bruker model AM spectrometer. The ^1H NMR spectrum represents 128 co added transients collected with a 4 μsec pulse and a relaxation delay time of 5 seconds. The free induction decay (FID) was exponentially multiplied with a 0.1 Hz Lorentzian line broadening factor to improve the signal-to-noise ratio. The NMR spectrum was processed utilizing GRAMS software, version 5.24. Samples were dissolved in dimethyl sulfoxide- d_6 .

The scope of this invention can be understood with reference to the appended claims.

6.8 Intrinsic Dissolution and Solubility Studies

Intrinsic dissolution experiments were conducted on Form A (anhydrous), Form B (hemihydrate), and Form E (dihydrate) of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione. Equilibrium solubility experiments were conducted on Forms A and B. Aliquots were analyzed by ultraviolet-visible spectrophotometry, and the solids remaining from each experiment were analyzed by X-ray powder diffraction (XRPD).

6.8.1 Experimental

6.8.1.1 Dissolution

Dissolution experiments were carried out in a VanKel VK6010-8 dissolution apparatus equipped with a VK650A heater/circulator. An intrinsic dissolution apparatus (Woods apparatus) was used. Samples were compressed at 1.5 metric tons (1000 psi) for 1 min using the Woods apparatus in a hydraulic press, giving a sample surface of 0.50 cm^2 . A dissolution medium consisting of 900 mL HCl buffer, pH 1.8, with 1% sodium lauryl sulfate, was used for each experiment. The medium was degassed by vacuum filtration through a 0.22- μm nylon filter disk and maintained at 37° C. The appa-

ratus was rotated at 50 rpm for each experiment. Aliquots were filtered immediately using 0.2- μm nylon syringe filters. In some cases, the undissolved solids were recovered and analyzed by X-ray powder diffraction (XRPD).

6.8.1.2 Solubility

Equilibrium solubility experiments were conducted in a 100-mL, three-neck, round-bottom flask immersed in a constant temperature oil bath maintained at 25° C. A solid sample of 400-450 mg was stirred in 50 mL of dissolution medium (HCl buffer, pH 1.8, with 1% sodium lauryl sulfate) using a mechanical stir rod. Aliquots were filtered using 0.2- μm nylon syringe filters and immediately diluted 1 mL→50 mL, then 5 mL→25 mL with dissolution medium in Class A glassware, a final dilution factor of 250.

6.8.1.3 UV-Vis Spectrophotometry

Dissolution and solubility samples solutions were analyzed by a Beckman DU 640 single-beam spectrophotometer. A 1.000-cm quartz cuvette and an analysis wavelength of 228.40 nm were utilized. The detector was zeroed with a cuvette filled with dissolution medium.

6.8.1.4 X-Ray Powder Diffraction

XRPD analyses were carried out on a Shimadzu XRD-6000 X-ray powder diffractometer using Cu $K\alpha$ radiation. The instrument is equipped with a fine focus X-ray tube. The tube power and amperage were set at 40 kV and 40 mA, respectively. The divergence and scattering slits were set at 1° and the receiving slit was set at 0.15 mm. Diffracted radiation was detected by a NaI scintillation detector. A theta-two theta continuous scan at 3°/min (0.4 sec/0.02° step) from 2.5 to 40° 2 θ was used. A silicon standard was analyzed each day to check the instrument alignment. Samples were packed in an aluminum holder with silicon insert.

6.8.2 Results

The results of these solubility and intrinsic studies are summarized in Table 6. Both the solubility and dissolution experiments were conducted in a medium of HCl buffer, pH 1.8, containing 1% sodium lauryl sulfate. Form A was found to be unstable in the medium, converting to Form E. The solubilities of Forms A, B, and E were estimated to be 6.2, 5.8, and 4.7 mg/mL, respectively. The dissolution rates of Forms A, B, and E were estimated to be 0.35, 0.34, and 0.23 mg/mL, respectively.

6.8.2.1 UV-Vis Spectrophotometry Method Development

A UV-V is scan of the dissolution medium (blanked with an empty cuvette) was done to identify any interfering peaks. A small peak at 225 nm was present as shown in FIG. 47.

Solutions of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione at varying concentrations were analyzed by UV-V is spectrophotometry. A preliminary scan of a 1.0 mg/mL solution was done, with the instrument blanked with dissolution medium. The solution was highly absorbing and noisy from 200-280 nm, making dilution necessary.

A 0.04 mg/mL solution of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione was then scanned from 200-300 nm. The plot was still noisy between 200 and 230 nm as shown in FIG. 48. The sample was further diluted to 0.008 mg/mL. A wavelength scan of 200-350 nm for this sample showed a peak at 228.4 nm with no interference, as shown in FIG. 49. Therefore, a wavelength of 228.4 was chosen for analysis of the solubility and dissolution samples.

A six-point calibration curve was generated with standards of the following concentrations: 0.001 mg/mL, 0.002 mg/mL, 0.005 mg/mL, 0.010 mg/mL, 0.015 mg/mL, and 0.020 mg/mL (Notebook 569-90). A linearity coefficient of $R^2=0.9999$ was obtained as shown in FIG. 50.

6.8.2.2 Solubility

A sample consisting of 449.4 mg Form A was slurried in dissolution medium. Particle size was not controlled. Aliquots were taken at 7, 15, 30, 60, 90, and 150 min. The concentration reached 6.0 mg/mL by the first time point. The highest concentration reached was 6.2 mg/mL, at 30 min. From that point the concentration decreased, reaching 4.7 mg/mL at 150 min as in FIG. 51. The solids remaining at the final time point were analyzed by XRPD and found to be Form E as shown in Table 7. No peaks attributed to Form A can be seen in the pattern. Since the concentration did not plateau at 4.7 mg/mL, the solubility of Form E may be lower than that.

A sample consisting of 401.4 mg Form B was slurried in dissolution medium. Particle size was not controlled. Aliquots were taken at 7, 15, 30, 60, 90, 180, 420, and 650 min. Form B dissolved much more slowly than Form A, reaching 3.3 mg/mL in 90 min. The concentration stabilized at 5.6-5.7 mg/mL at the final three time points as in FIG. 52. The remaining solids were shown to be Form B as in Table 7, suggesting Form B has good stability in water.

A summary of the solubilities is given in Table 6. The amounts dissolved at each time point are shown in Tables 8 and 9.

TABLE 6

Summary of Results				
Form	Solubility	Intrinsic Dissolution #1	Intrinsic Dissolution #2	Average Intrinsic Dissolution Rate
Form A	6.2 mg/mL	0.35	0.22 ^a	0.29 ^a
Form B	5.8 mg/mL	0.35	0.32	0.34
Form E	4.7 mg/mL	0.21	0.25	0.23

^aThe Form A dissolution experiment #2 may have converted to Form E on the surface of the disk, skewing the average rate lower.

TABLE 7

Experimental Details	
Experiment	Final Form
Pressed Form A	A
Pressed Form B	B
Form A Solubility	E
Form B Solubility	B
Form A Dissolution	—
Form A Dissolution	A
Form B Dissolution	—
Form B Dissolution	B
Form E Dissolution	E
Form E Dissolution	—

TABLE 8

Form A Solubility	
Time Point (min)	Concentration (mg/mL)
7	6.00
15	6.11
30	6.16
60	6.10
90	5.46
150	4.73

TABLE 9

Form B Solubility	
Time Point (min)	Concentration (mg/mL)
7	1.63
15	2.14
30	2.33
60	2.94
90	3.34
180	5.67
420	5.76
650	5.61

6.8.2.3 Intrinsic Dissolution

Approximately 200 mg each of Forms A and B were compressed into disks in the Woods apparatus using 2 metric tons of pressure. The samples were subsequently scraped out, ground gently, and analyzed by XRPD. The study showed that compression and grinding does not cause a form change in either case. (See Table 7).

Two preliminary dissolution runs were performed. The disks fractured to some extent in both experiments, compromising the requirement of constant surface area.

The first experiment of intrinsic dissolution that strictly followed the USP chapter on intrinsic dissolution utilized approximately 150 mg each of Forms A and B. Seven aliquots, beginning at 5 min and ending at 90 min, were taken to maintain sink conditions. The experiment resulted in linear dissolution profiles, with a rate of 0.35 mg per cm² per minute for both forms. The Form E experiment was done later under the same conditions and added to the graph for comparison. (See FIG. 53). The Form E dissolution rate was 0.21 mg per cm² per minute, significantly lower than the dissolution rate of Forms A and B. This is in line with expectations based on the solubility data. The crystal form of the remaining solids did not change in any case.

The second experiment utilized approximately 250 mg each of Forms A and B. The Form E experiment (135 mg) was done later and added to the graph for comparison. (See FIG. 54). Nine aliquots were taken, beginning at 5 min and ending at 150 min. The dissolution rates were 0.22, 0.32, and 0.25 mg per cm² per minute, respectively, for Forms A, B, and E. The dissolution rate for Form A in this experiment was low, while the rates for Forms B and E were similar to those found in the first experiment. It is believed that in this case, a thin layer of the Form A sample disk may have converted to Form E upon exposure to water. This is supported by the evidence of rapid conversion of Form A to Form E in the solubility experiment. The diffraction pattern of the undissolved solids does not indicate a form change. However, the bulk of the sample disk is not exposed to water. Therefore, the true intrinsic dissolution rate of Form A is believed to be close to 0.35 mg per cm² per minute. An insufficient quantity of Form A was available to repeat the experiment.

A summary of the intrinsic dissolution rates is given in Table 6. The amounts dissolved at each time point are summarized in Tables 10 and 11.

TABLE 10

Intrinsic Dissolution Experiment #1 Results			
Time Point	Form A ^a	Form B ^a	Form E ^a
5 min	5.76	10.80 ^b	2.70
10 min	7.73	6.85	4.13

TABLE 10-continued

Intrinsic Dissolution Experiment #1 Results			
Time Point	Form A ^a	Form B ^a	Form E ^a
20 min	11.31	10.25	6.96
30 min	15.59	14.35	9.60
45 min	21.98	20.57	12.57
60 min	27.11	25.70	15.16
90 min	34.17	34.34	20.82

^aResults are reported as Cumulative Amount Dissolved per Unit Area (mg/cm2)
^bThis date point not included in graph since the value is higher than the next two data points.

TABLE 11

Intrinsic Dissolution Experiment #2 Results			
Time Point	Form A ^a	Form B ^a	Form E ^a
5 min	4.50	5.04	3.06
10 min	5.22	6.12	4.31
20 min	7.54	7.73	11.40
30 min	11.46	12.72	11.93
45 min	15.01	17.33	14.72
60 min	18.38	21.93	18.52
90 min	24.38	31.64	26.24
120 min	30.35	41.31	33.56
150 min	35.26	49.54	40.82

^aResults are reported as Cumulative Amount Dissolved per Unit Area (mg/cm2)

6.9 Analyses of Mixtures of Polymorphs

This invention encompasses mixtures of different polymorphs. For example, an X-ray diffraction analysis of one production sample yielded a pattern that contained two small peaks seen at approximately 12.6° and 25.8° 2θ in addition to those representative of Form B. In order to determine the composition of that sample, the following steps were performed.

- 1) Matching of the new production pattern to known forms along with common pharmaceutical excipients and contaminants;
- 2) Cluster analysis of the additional peaks to identify if any unknown phase is mixed with the original Form B;
- 3) Harmonic analysis of the additional peaks to identify if any preferred orientation may be present or if any changes in the crystal habit may have occurred; and
- 4) Indexing of the unit cells for both Form B and the new production sample to identify any possible crystallographic relationships.

Based on these tests, which can be adapted for the analysis of any mixture of polymorphs, it was determined that the sample contained a mixture of polymorph forms B and E.

6.10 Dosage Form

Table 12 illustrates a batch formulation and single dosage formulation for a 25 mg single dose unit of a polymorphic form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione.

TABLE 12

Formulation for a 25 mg capsule			
Material	Percent By Weight	Quantity (mg/tablet)	Quantity (kg/batch)
Polymorphic Form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione	40.0%	25 mg	16.80 kg
Pregelatinized Corn Starch, NF	59.5%	37.2 mg	24.99 kg
Magnesium Stearate	0.5%	0.31 mg	0.21 kg
Total	100.0%	62.5 mg	42.00 kg

The pregelatinized corn starch (SPRESS B-820) and polymorphic form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione components are passed through a screen (i.e., a 710 μm screen) and then loaded into a Diffusion Mixer with a baffle insert and blended for about 15 minutes. The magnesium stearate is passed through a screen (i.e., a 210 μm screen) and added to the Diffusion Mixer. The blend is then encapsulated in capsules using a Dosator type capsule filling machine.

The entire scope of this invention is not limited by the specific examples described herein, but is more readily understood with reference to the appended claims.

What is claimed is:

- 1. A solid form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione comprising crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione hemihydrate, wherein the crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione hemihydrate is present at greater than about 80% by weight of the solid form.
- 2. A solid form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione comprising crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione hemihydrate, wherein the crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione hemihydrate is present at greater than about 90% by weight of the solid form.
- 3. A solid form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione comprising crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione hemihydrate, wherein the crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione hemihydrate is present at greater than about 95% by weight of the solid form.
- 4. A solid form of 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione comprising crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione hemihydrate, wherein the crystalline 3-(4-amino-1-oxo-1,3 dihydro-isoindol-2-yl)-piperidine-2,6-dione hemihydrate is present at greater than about 97% by weight of the solid form.
- 5. A pharmaceutical composition comprising a therapeutically effective amount of the solid form of claim 1, 2, 3, or 4, and a pharmaceutically acceptable excipient or carrier.
- 6. The pharmaceutical composition of claim 5, which is a single unit dosage form.
- 7. The pharmaceutical composition of claim 5, wherein the therapeutically effective amount is about 5 mg.
- 8. The pharmaceutical composition of claim 5, wherein the therapeutically effective amount is about 10 mg.
- 9. The pharmaceutical composition of claim 5, wherein the therapeutically effective amount is about 25 mg.
- 10. The pharmaceutical composition of claim 5, wherein the therapeutically effective amount is about 50 mg.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 7,855,217 B2
APPLICATION NO. : 12/335395
DATED : December 21, 2010
INVENTOR(S) : Jaworsky et al.

Page 1 of 11

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Please replace Drawing Sheets 15, 26, 31, 32, 33, 35, 36, 38, 39, and 40 (of 48) with the Replacement Drawing Sheets on the following pages of this Certificate of Correction:

Page 2 of 11: Replacement Drawing Sheet 15 of 48 (Fig. 15);

Page 3 of 11: Replacement Drawing Sheet 26 of 48 (Fig. 26);

Page 4 of 11: Replacement Drawing Sheet 31 of 48 (Fig. 31);

Page 5 of 11: Replacement Drawing Sheet 32 of 48 (Figs. 32 and 33);

Page 6 of 11: Replacement Drawing Sheet 33 of 48 (Figs. 34 and 35);

Page 7 of 11: Replacement Drawing Sheet 35 of 48 (Figs. 37 and 38);

Page 8 of 11: Replacement Drawing Sheet 36 of 48 (Figs. 39 and 40);

Page 9 of 11: Replacement Drawing Sheet 38 of 48 (Figs. 42 and 43);

Page 10 of 11: Replacement Drawing Sheet 39 of 48 (Figs. 44 and 45);

Page 11 of 11: Replacement Drawing Sheet 40 of 48 (Fig. 46).

Signed and Sealed this
Third Day of May, 2011

A handwritten signature in black ink that reads "David J. Kappos". The signature is written in a cursive, flowing style with a large initial "D" and a stylized "K".

David J. Kappos
Director of the United States Patent and Trademark Office

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Dec. 21, 2010

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TGA (TOP) AND DSC (BOTTOM) OF FORM C

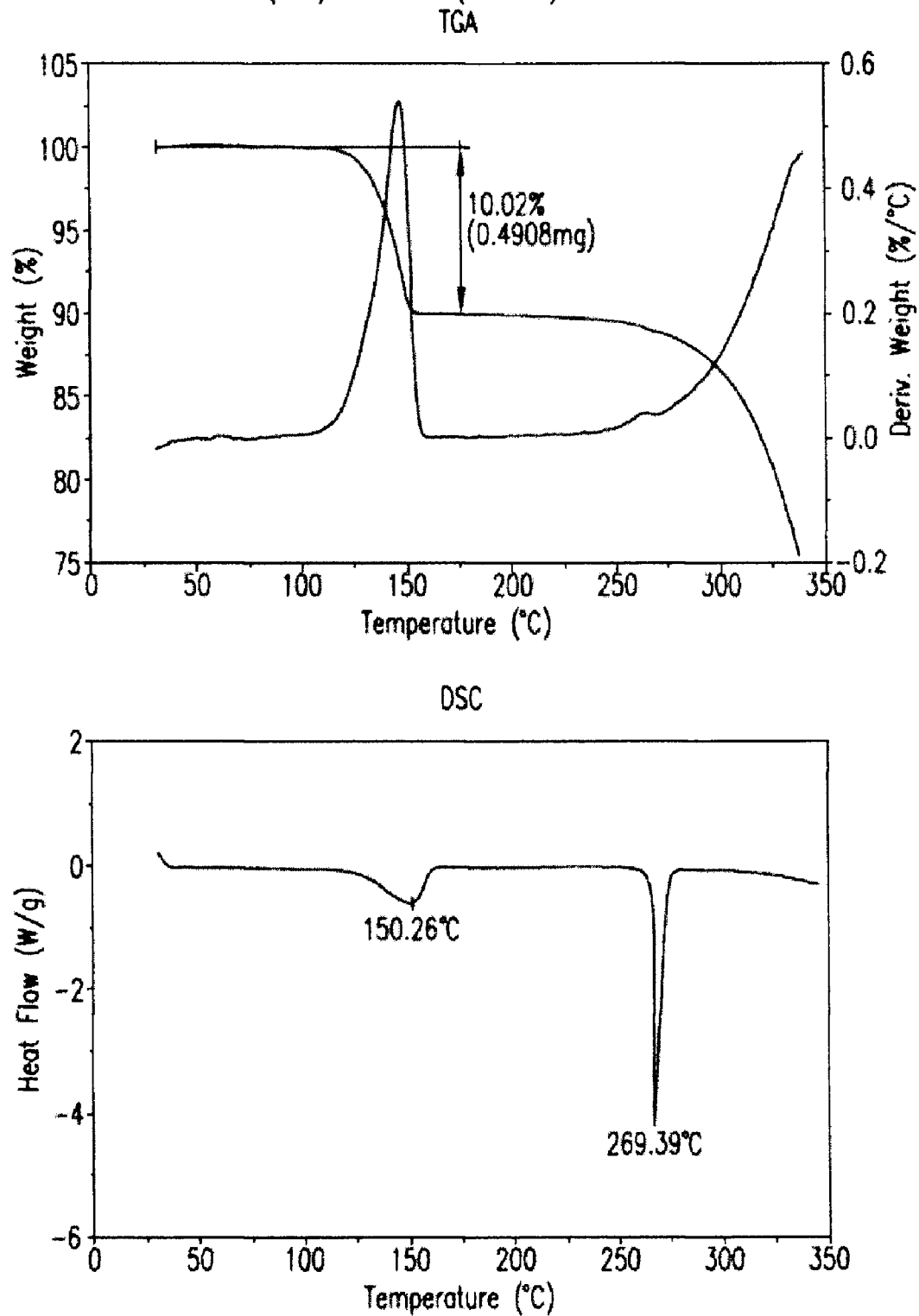


FIG.15

CERTIFICATE OF CORRECTION (continued)

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Sheet 26 of 48

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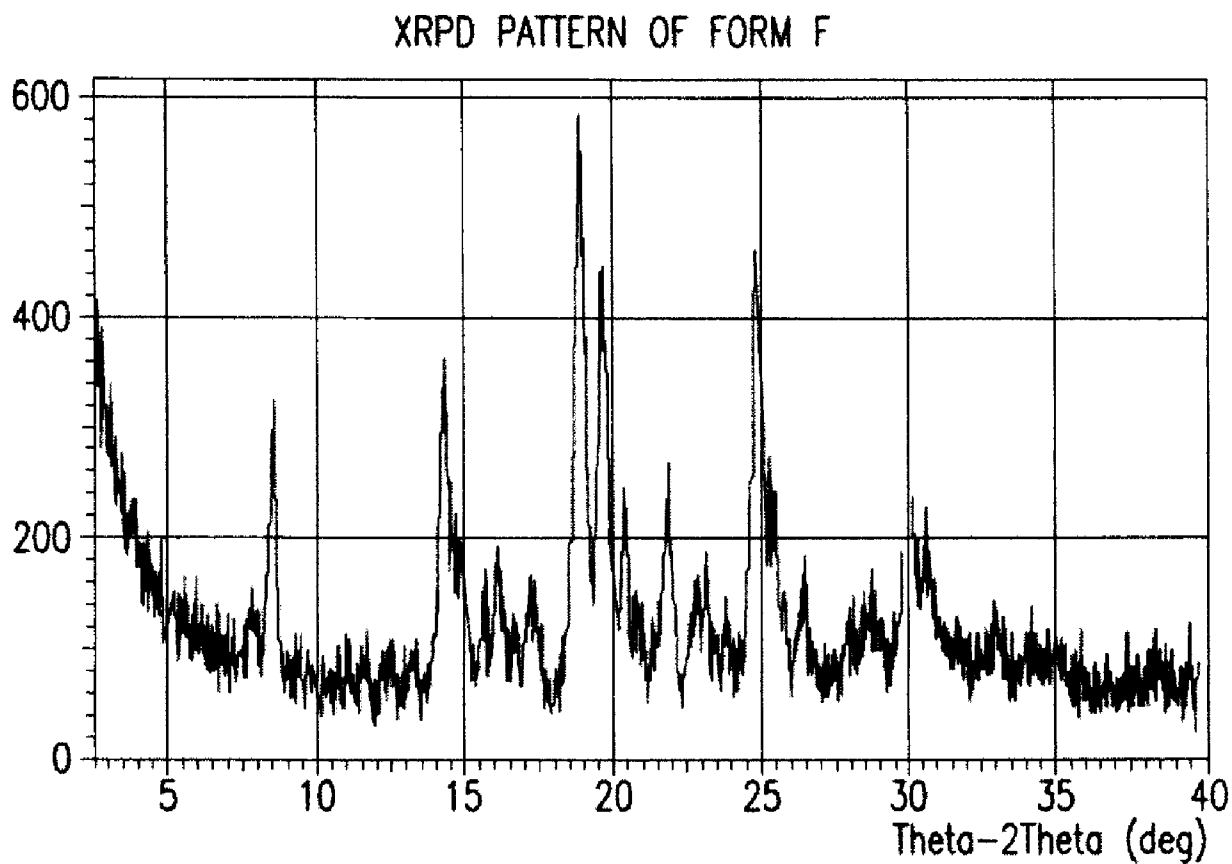


FIG.26

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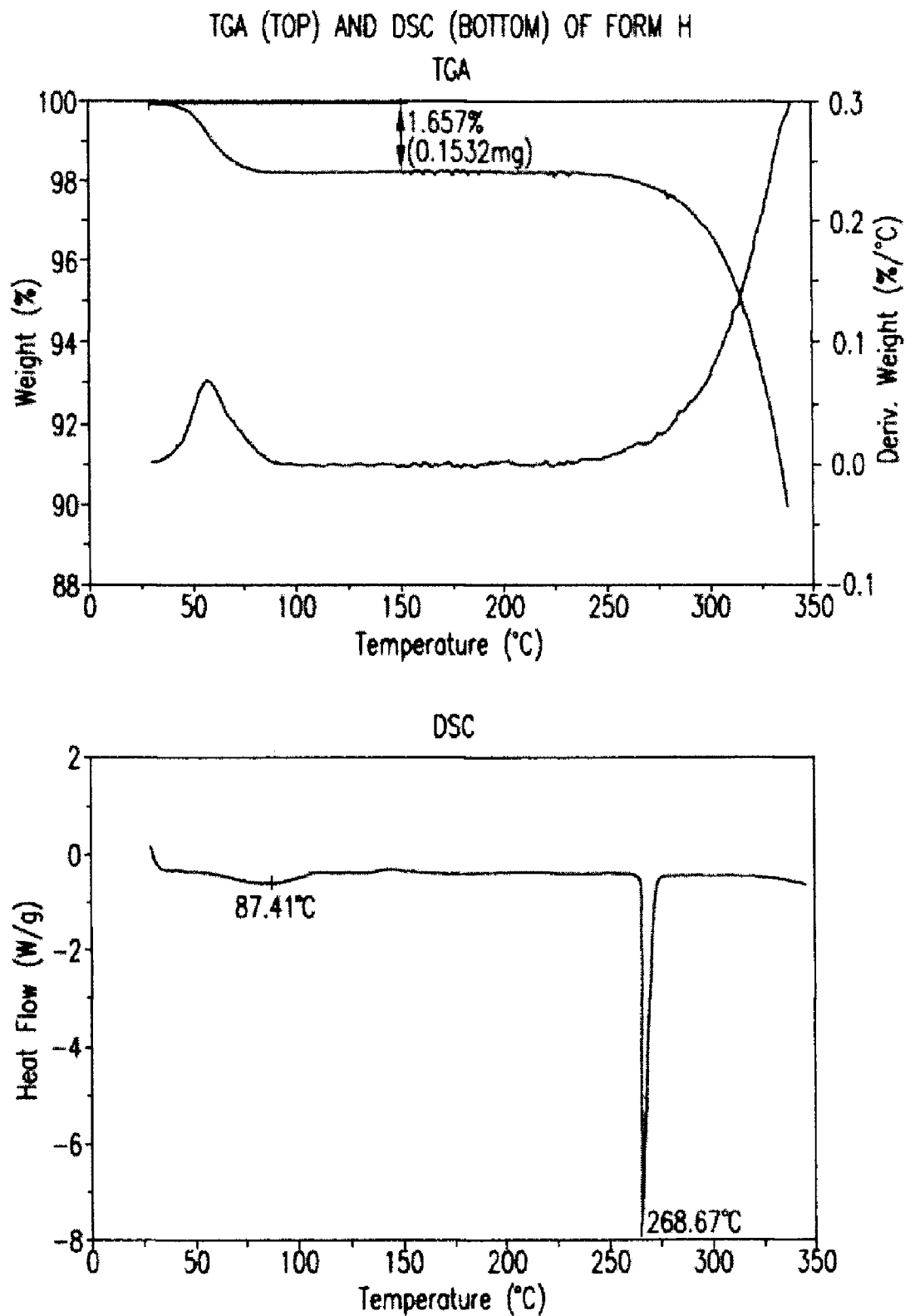


FIG.31

CERTIFICATE OF CORRECTION (continued)

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XRPD PATTERN OF POLYMORPH B

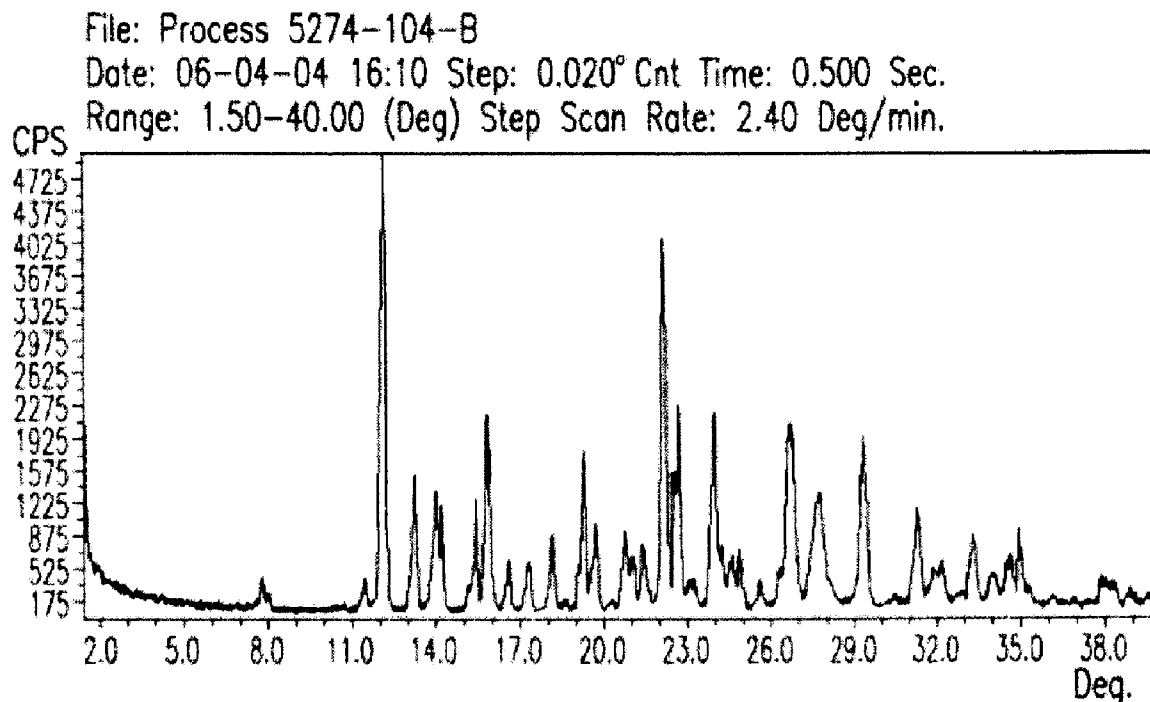


FIG.32

XRPD PATTERN OF POLYMORPH B

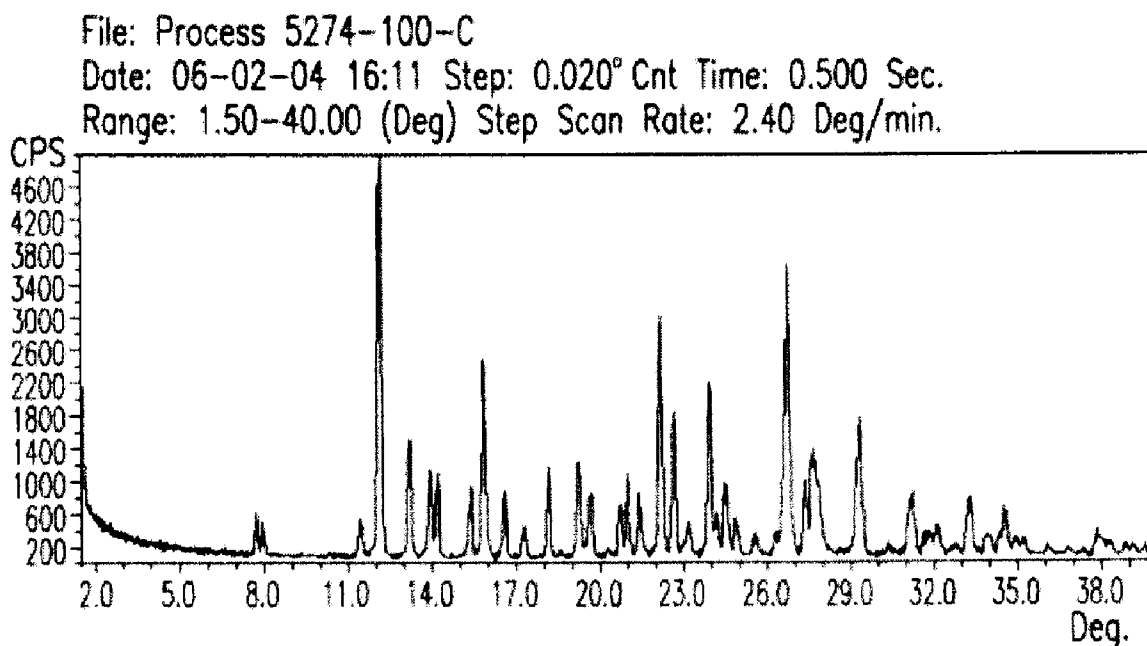


FIG.33

CERTIFICATE OF CORRECTION (continued)

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XRPD PATTERN OF POLYMORPH B

File: Process 5222-157-C

Date: 06/04/04 15:07 Step: 0.020° Cnt Time: 0.500 Sec.

Range: 1.50-40.00 (Deg) Step Scan Rate: 2.40 Deg/min.

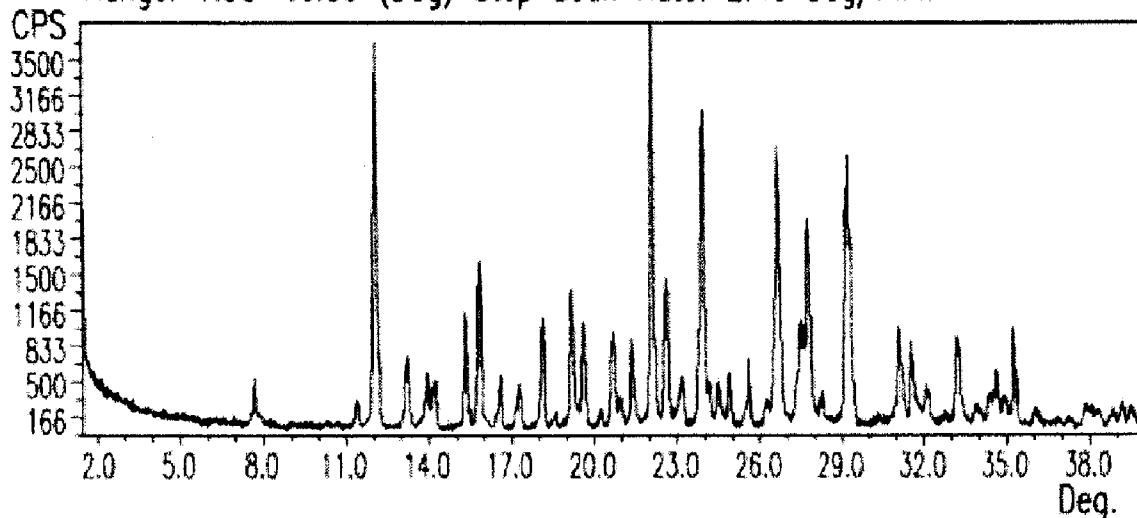


FIG.34

XRPD PATTERN OF POLYMORPH E

File: Process 5222-152-B Form E

Date: 05/21/04 10:46 Step: 0.020° Cnt Time: 0.500 Sec.

Range: 1.50-40.00 (Deg) Step Scan Rate: 2.40 Deg/min.

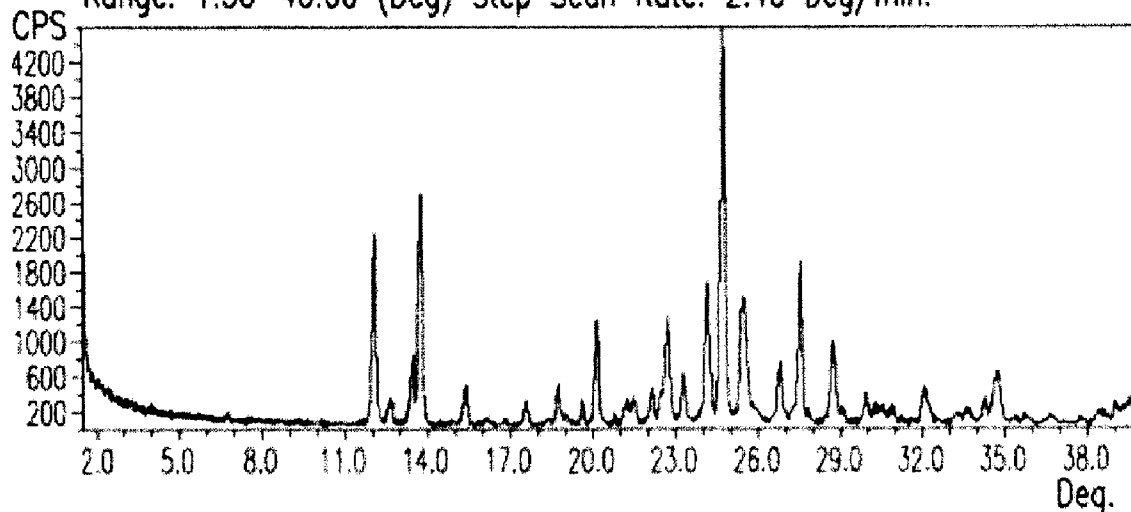


FIG.35

CERTIFICATE OF CORRECTION (continued)

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TGA CURVE OF POLYMORPH B
Sample: 5274-104-B TGA
Size 7.8320mg Run Date: 09-Jun-04 17:04
Method: Ramp Instrument: TGA 0.500 V5.3 Build 171

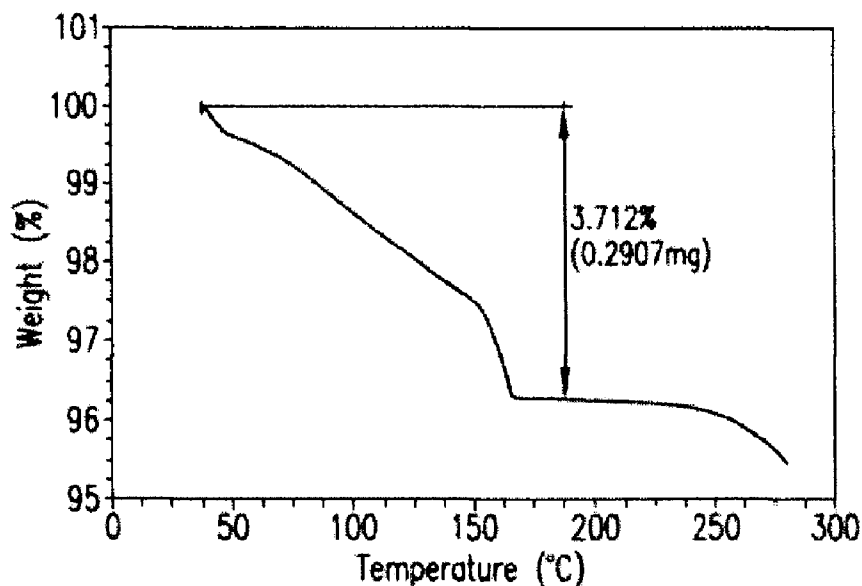


FIG.37

TGA CURVE OF POLYMORPH B
Sample: 5274-100-C TGA
Size 10.9430mg Run Date: 03-Jun-04 11:20
Method: Ramp Instrument: TGA 0.500 V5.3 Build 171
Comment: Evotec Batch 1675C H2O

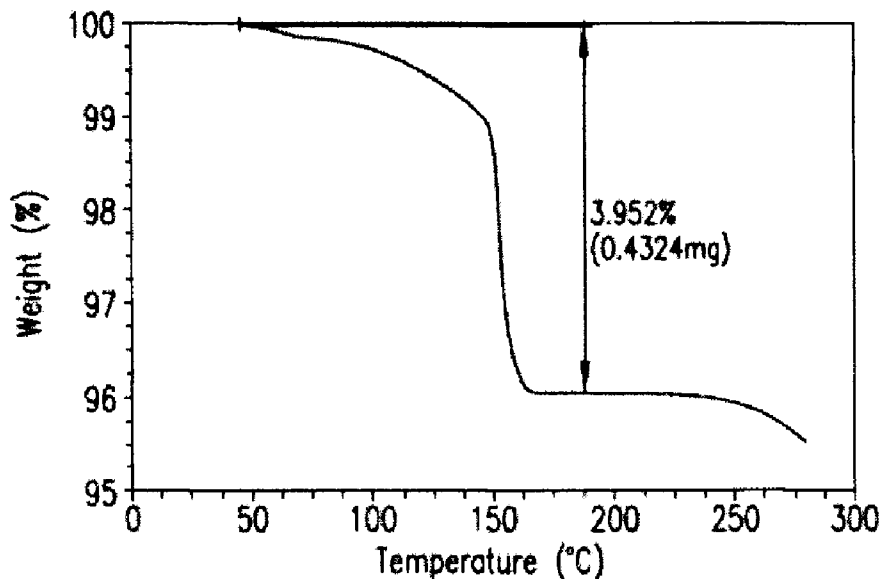


FIG.38

CERTIFICATE OF CORRECTION (continued)

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TGA CURVE OF POLYMORPH B
TGA
Sample: 5222-157-C
Size: 24.4610mg
Method: Ramp
Comment: Evotec Batch 17
Run Date: 07-Jun-04 09:46
Instrument: TGA 0.500 V5.3 Build 171

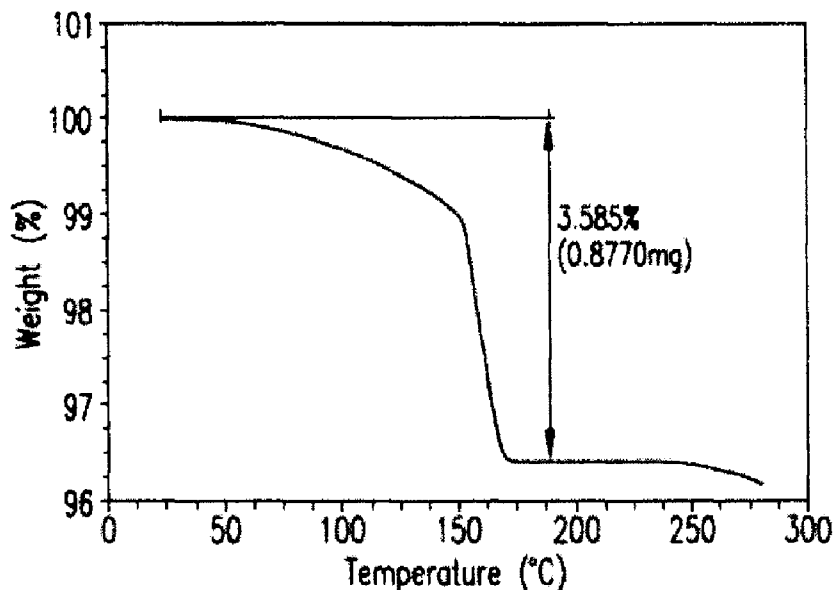


FIG.39

TGA CURVE OF POLYMORPH E
TGA
Sample: 5222-152-B
Size: 11.3850mg
Method: Ramp
Comment: Form E
Run Date: 21-May-04 09:34
Instrument: TGA 0.500 V5.3 Build 171

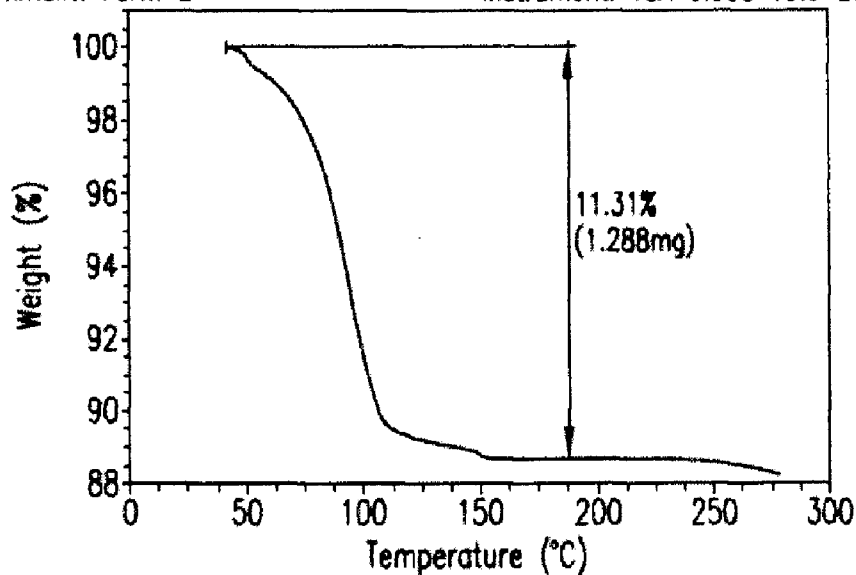


FIG.40

CERTIFICATE OF CORRECTION (continued)

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DSC OF POLYMORPH B
DSC
Sample: 5274-104-B
Size: 0.0000mg
Method: Cell constant calibration
Comment: OAI batch 15 22b
Run Date: 07-Jun-04 11:30
Instrument: DSC Q 1000 V7.3 Build 249

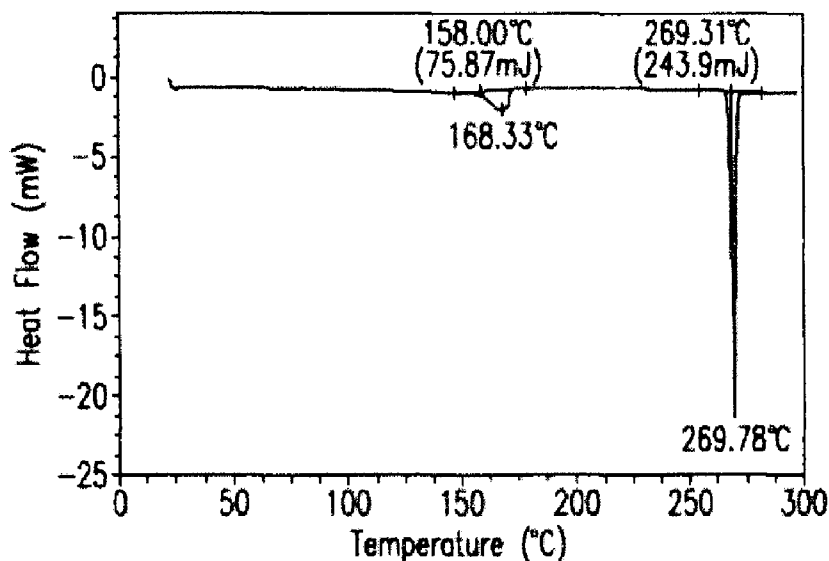


FIG.42

DSC OF POLYMORPH B
DSC
Sample: 5274-100-C
Size: 0.0000mg
Method: Cell constant calibration
Comment: Evotec Batch 1675C 10vol H2O 24h 3h dry
Run Date: 02-Jun-04 17:01
Instrument: DSC Q 1000 V7.3 Build 249

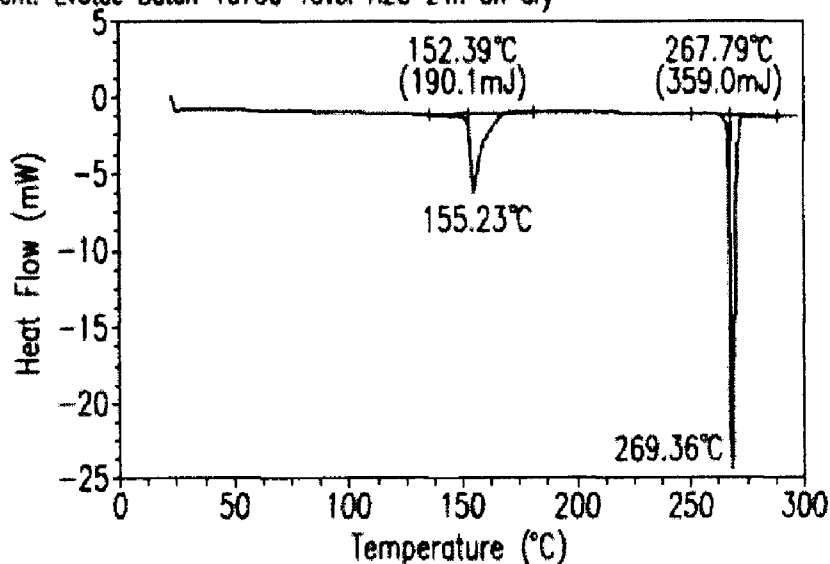


FIG.43

CERTIFICATE OF CORRECTION (continued)

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DSC OF POLYMORPH B
DSC

Sample: 5222-157-C
Size: 0.0000mg
Method: Cell constant calibration
Comment: OAI batch 17

Run Date: 07-Jun-04 09:45
Instrument: DSC Q 1000 V7.3 Build 249

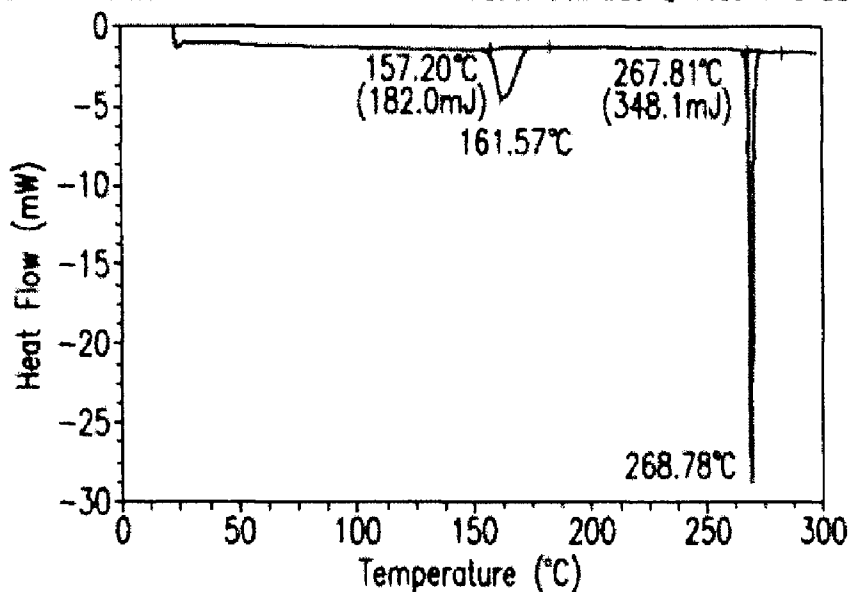


FIG.44

DSC OF POLYMORPH E
DSC

Sample: 5222-152-B
Size: 3.4500mg
Method: Cell constant calibration
Comment: Evotec batch 15 Form E

Run Date: 21-May-04 09:32
Instrument: DSC Q 1000 V7.3 Build 249

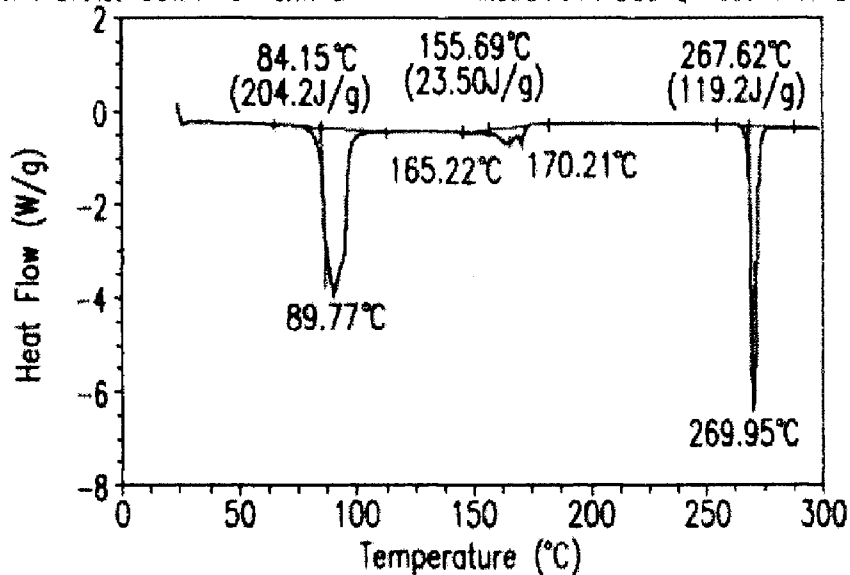


FIG.45

CERTIFICATE OF CORRECTION (continued)

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DSC OF POLYMORPH MIXTURE
DSC

Sample: 5222-161-A
Size: 0.0000mg
Method: Cell constant calibration
Comment: OAI batch 15

Run Date: 11-Jun-04 12:44
Instrument: DSC Q 1000 V7.3 Build 249

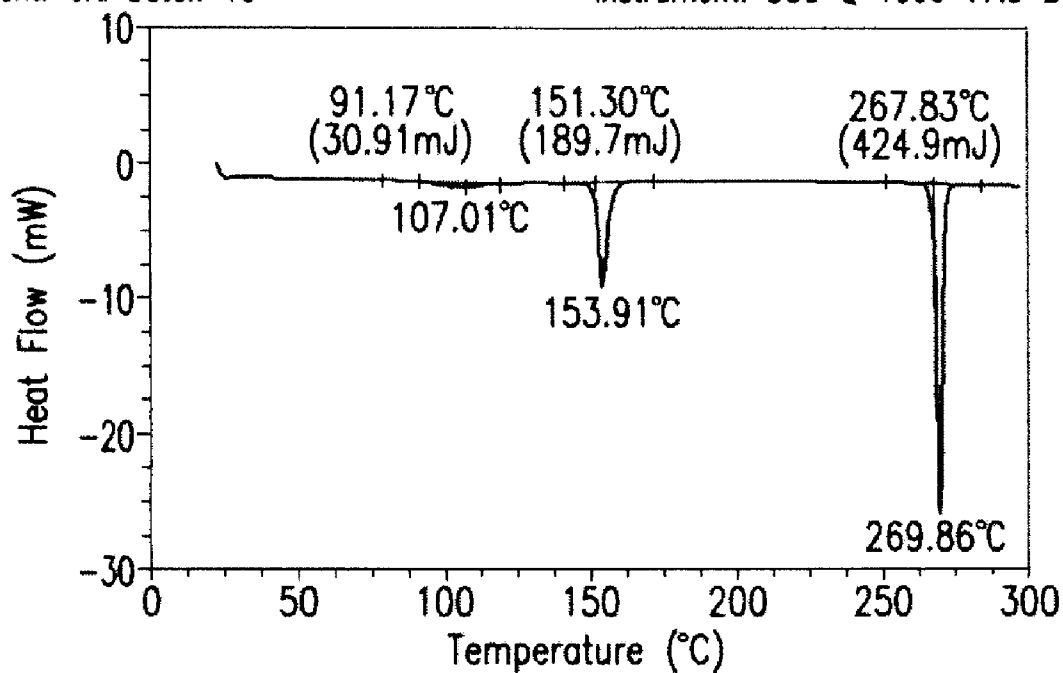


FIG.46

EXHIBIT H



US007468363B2

(12) **United States Patent**
Zeldis

(10) **Patent No.:** **US 7,468,363 B2**
(45) **Date of Patent:** ***Dec. 23, 2008**

(54) **METHODS FOR TREATMENT OF CANCERS USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE**

(75) Inventor: **Jerome B. Zeldis**, Princeton, NJ (US)

(73) Assignee: **Celgene Corporation**, Summit, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 161 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/102,742**

(22) Filed: **Apr. 8, 2005**

(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**
A61K 31/33 (2006.01)
A61K 31/55 (2006.01)

(52) **U.S. Cl.** **514/183**; 514/217.08; 514/217.09

(58) **Field of Classification Search** 514/321, 514/183, 217.08, 217.09

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,536,809 A 10/1970 Applezweig
3,598,123 A 8/1971 Zaffaroni et al.
3,845,770 A 11/1974 Theeuwes et al.
3,916,899 A 11/1975 Theeuwes et al.
4,008,719 A 2/1977 Theeuwes et al.
4,810,643 A 3/1989 Souza
4,999,291 A 3/1991 Souza
5,059,595 A 10/1991 Le Grazie
5,073,543 A 12/1991 Marshall et al.
5,120,548 A 6/1992 McClelland et al.
5,134,127 A 7/1992 Stella et al.
5,229,496 A 7/1993 Deeley et al.
5,354,556 A 10/1994 Sparks et al.
5,385,901 A 1/1995 Kaplan et al.
5,391,485 A 2/1995 Deeley et al.
5,393,870 A 2/1995 Deeley et al.
5,528,823 A 6/1996 Rudy, Jr. et al.
5,580,755 A 12/1996 Souza
5,591,767 A 1/1997 Mohr et al.
5,593,990 A 1/1997 D'Amato
5,629,327 A 5/1997 D'Amato
5,635,517 A 6/1997 Muller et al.
5,639,476 A 6/1997 Oshlack et al.
5,674,533 A 10/1997 Santus et al.
5,698,579 A 12/1997 Muller

5,712,291 A 1/1998 D'Amato
5,731,325 A 3/1998 Andrulis, Jr. et al.
5,733,566 A 3/1998 Lewis
5,798,368 A 8/1998 Muller et al.
5,874,448 A 2/1999 Muller et al.
5,877,200 A 3/1999 Muller
5,929,117 A 7/1999 Muller et al.
5,955,476 A 9/1999 Muller et al.
6,020,358 A 2/2000 Muller et al.
6,071,948 A 6/2000 D'Amato
6,114,355 A 9/2000 D'Amato
6,140,346 A 10/2000 Andrulis, Jr. et al.
6,228,879 B1 5/2001 Green et al.
6,235,756 B1 5/2001 D'Amato
6,281,230 B1 8/2001 Muller et al.
6,316,471 B1 11/2001 Muller et al.
6,326,388 B1 12/2001 Man et al.
6,335,349 B1 1/2002 Muller et al.
6,380,239 B1 4/2002 Muller et al.
6,395,754 B1 5/2002 Muller et al.
6,403,613 B1 6/2002 Man et al.
6,420,414 B1 7/2002 D'Amato
6,458,810 B1 10/2002 Muller et al.
6,469,045 B1 10/2002 D'Amato
6,476,052 B1 11/2002 Muller et al.
6,518,298 B2 2/2003 Green et al.
6,555,554 B2 4/2003 Muller et al.
6,673,828 B1 1/2004 Green et al.

(Continued)

FOREIGN PATENT DOCUMENTS

WO WO 98/03502 1/1998

(Continued)

OTHER PUBLICATIONS

Gura (Science, 1997, 278:1041-1042).*

(Continued)

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Assistant Examiner—Alicia Hughes

(74) *Attorney, Agent, or Firm*—Jones Day

(57) **ABSTRACT**

Methods of treating a specific cancer or amyloidosis are disclosed. Specific methods encompass the administration of 3-(4-amino-1 oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2, 6-dione alone or in combination with a second active ingredient.

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U.S. PATENT DOCUMENTS

6,797,708	B2 *	9/2004	McKew et al.	514/228.2
6,903,104	B2 *	6/2005	Chen et al.	514/254.09
2001/0018445	A1	8/2001	Huang et al.	
2001/0056114	A1	12/2001	D'Amato	
2002/0035090	A1	3/2002	Zeldis et al.	
2002/0045643	A1	4/2002	Muller et al.	
2002/0052398	A1	5/2002	D'Amato	
2002/0054899	A1	5/2002	Zeldis	
2002/0061923	A1	5/2002	D'Amato	
2002/0128228	A1	9/2002	Hwu	
2002/0161023	A1	10/2002	D'Amato	
2002/0173658	A1	11/2002	Muller et al.	
2002/0183360	A1	12/2002	Muller et al.	
2003/0013739	A1	1/2003	Masferrer et al.	
2003/0028028	A1	2/2003	Man et al.	
2003/0045552	A1	3/2003	Robarge et al.	
2003/0069428	A1	4/2003	Muller et al.	
2003/0096841	A1	5/2003	Robarge et al.	
2003/0139451	A1	7/2003	Shah et al.	
2003/0144325	A1	7/2003	Muller et al.	
2003/0181428	A1	9/2003	Green et al.	
2003/0187024	A1	10/2003	D'Amato	
2003/0191098	A1	10/2003	D'Amato	
2003/0235909	A1	12/2003	Hariri et al.	
2004/0029832	A1	2/2004	Zeldis	
2004/0067953	A1 *	4/2004	Stein et al.	514/251
2004/0077685	A1	4/2004	Figg et al.	
2004/0077686	A1	4/2004	Dannenberg et al.	
2004/0087546	A1	5/2004	Zeldis	
2004/0091455	A1	5/2004	Zeldis	
2004/0122052	A1	6/2004	Muller et al.	
2004/0127545	A1	7/2004	D'Amato et al.	
2004/0147558	A1	7/2004	Treston et al.	
2004/0266809	A1	12/2004	Emanuel et al.	
2005/0049265	A1	3/2005	Adams	

FOREIGN PATENT DOCUMENTS

WO	WO 98/54170	12/1998
WO	WO 01/70275	9/2001
WO	WO 01/87307	11/2001
WO	WO 02/059106	8/2002
WO	WO 02/064083	8/2002
WO	WO 03/086373	10/2003

OTHER PUBLICATIONS

Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39).*

Alexanian et al., 2004, "VTD (Velcade, thalidomide, dexamethasone) as primary therapy for newly-diagnosed multiple myeloma," Am. Soc. Hematol. 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract #210.

Anderson, 2000, "Thalidomide: Therapeutic potential in hematologic malignancies," Seminars in Hematology 37(1 Supp 3): 1-4.

Attal et al., 2004, "Maintenance treatment with thalidomide after autologous transplantation for myeloma: First analysis of a prospective randomized study of the Intergroupe Francophone du Myelome (IFM 99 02)," Am. Soc. Hematol. 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract #535.

Bach, 1963, "Thalidomide in Cancer Chemotherapy," *The Lancet*, No. 1271, p. 71.

Bach, 1963, "Studies on the Possible Anti-Neoplastic Effect of Thalidomide," *Acta Pathologica Et Microbiologica Scandinavica* 59:491-499.

Bernardeschi et al., 2003, J. Exp. Clin. Cancer Res. 22(4):129-133.

Cartensen, 1995, *Drug Stability: Principles & Practice*, 2nd ed., Marcel Dekker, New York, NY pp. 379-380.

Chaundhry, 1966, *Cancer Research*, "Effect of Prednisolone and Thalidomide on Induced Submandibular Gland Tumors in Hamster," 26(part 1)1884-86.

Corral et al., 1999, "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha," J. Immunol. 163(1):380-386.

Corral et al., 1999, "Immunomodulation by thalidomide and thalidomide analogues," Ann. Rheum. Dis. 58(Suppl 1):1107-1113.

Craig et al., 1967, "Potential anticancer agents. III. 2-phthalimidoaldehydes and derivatives," Potential Anticancer Agents III 10:1071-1073.

D'Amato et al., 2001, "Mechanism of action of thalidomide and 3-aminothalidomide in multiple myeloma," Semin. Oncol. 28:597-601.

D'Amato et al., 1994, "Thalidomide is an Inhibitor of Angiogenesis", Proc. Natl. Acad. Sci. 91:4082-4085.

Davies et al., 2001, "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma," Blood 98(1):210-216.

De et al., 1976, "Hansch analysis for some antineoplastic glutarimides," J. Indian Chem. Soc. I.III: 825-826.

De et al., 1976, "Possible antineoplastic agents: III. Synthesis of 6-alkyl-2-[4'-methoxyphthalimido] and 6-alkyl-3-[3'-4'-dimethoxyphenyl] glutarimides," J. Indian Chem. Soc. I.III:1122-1125.

Dimopoulos et al., 2004, "Primary treatment with pulsed melphalan, dexamethasone, thalidomide (MDT) for symptomatic patients with multiple myeloma ≥ 75 years of age," Am. Soc. Hematol. 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract #1482.

DiPaolo, 1963, "Effect of Thalidomide on a Variety of Transplantable Tumors," *Cancer Chemotherapy Reports* No. 29, p. 99-102.

DiPaolo, 1963, "In vitro Test Systems for Cancer Chemotherapy, II. Correlation of in vitro Inhibition of Dehydrogenase and Growth with in vivo Inhibition of Ehrlich Ascites Tumor," *Proceedings of the Society for Experimental Biology & Medicine*, 114:384-387.

DiPaolo, 1964, "Thalidomide: Effects on Ehrlich Ascites Tumor Cells in vitro" Science 144:1583.

Dredge et al., 2002, "Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects," Br. J. Cancer 87(10):1166-1172.

Eisen et al., 2000, "Continuous low dose Thalidomide: a phase II study in advanced melanoma, renal cell, ovarian and breast cancer," Br. J. Cancer 82(4):812-817.

Fakhouri et al., 2004, "Thalidomide in patients with multiple myeloma and renal failure," Br. J. Haematol. 125:90-102.

Fenk et al., 2005, "Single-agent thalidomide for treatment of first relapse following high-dose chemotherapy in patients with multiple myeloma," Leukemia 19(1):156-159.

Folkman et al., 1983, "Angiogenesis inhibition and tumor regression caused by heparin or a heparin fragment in the presence of cortisone," Science 221(4612):719-725.

Gershbein, 1991, "The thalidomide analog, EM 12, enhances 1,2-dimethylhydrazine-induction of rat colon adenocarcinomas," Cancer Letters 60: 129-133.

Grabstald et al., 1965, "Clinical experiences with thalidomide in patients with cancer," Clinical Pharmacology and Therapeutics 6:298-302.

Gupta et al., 2001, "Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications," Leukemia 15(12):1950-1961.

Haslett et al., 2003, "Thalidomide and a thalidomide analogue drug costimulate virus-specific CD8+ T cells in vitro," J. Infect. Dis. 187(6):946-955.

He et al., 1993, "Synthesis of thalidomide analogs and their biological potential for treatment of graft versus host disease (GVHD)," 206th Am. Chem. Soc. Natl. Meet. Chicago, IL Med Chem. Abstract 216.

Hideshima et al., 2000, "Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy," Blood 96(9):2943-2950.

Jonsson, 1972, "Chemical Structure and Teratogenic Properties," Acta Pharm., pp. 521-542.

Lentzsch et al., 2003, "Immunomodulatory analogs of thalidomide inhibit growth of Hs Sultan cells and angiogenesis in vivo," Leukemia 17(1):41-44.

US 7,468,363 B2

Page 3

- Lentzsch et al., 2002, "S-3-amino-phthalimido-glutarimide inhibits angiogenesis and growth of B-cell neoplasias in mice", *Cancer Research* 62:2300-2305.
- Mauad, 1963, "Clinical Improvements Obtained in Advanced Cancer Patients with Treatment with Thalidomide Associated with Hormones," *Anais Paulistas de Medicina e Cirurgia* 86:13-40.
- Miyachi et al., 1997, "Novel biological response modifiers: phthalimides with tumor necrosis factor-alpha production-regulating activity," *J. Med. Chem.* 40:2858-2865.
- Muller et al., 1999, "Amino-substituted thalidomide analogs: potent inhibitors of TNF-alpha production," *Bioorg. Med. Chem. Lett.* 9(11):1625-1630.
- Muller et al., 1998, "Thalidomide analogs and PDE4 inhibition," *Bioorg. Med. Chem. Lett.* 8(19):2669-2674.
- Muller et al., 1996, "Structural modifications of thalidomide produce analogs with enhanced tumor necrosis factor inhibitory activity," *J. Med. Chem.* 39(17):3238-3240.
- Offidani et al., 2003, Thalidomide plus oral melphalan for advanced multiple myeloma: a phase II study. *Haematologica*. Dec. 2003;88(12):1432-1433.
- Olson et al., 1965, "Thalidomide (N-phthaloylglutamide) in the treatment of advanced cancer," *Clinical Pharmacology and Therapeutics* 6(3):292-297.
- Palumbo et al., 2004, "A prospective randomized trial of oral melphalan prednisone, thalidomide (MPT) vs. oral melphalan, prednisone (MP): An interim analysis," *Am. Soc. Hematol.* 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract #207.
- Penichet et al., 2001, "Antibody-cytokine fusion proteins for the therapy of cancer," *J. Immunol. Methods* 248(1-2):91-101.
- Physician's Desk Reference*, 2002, 56th ed., pp. 1755-1760.
- Raje et al., 1999, "Thalidomide—a revival story," *N. Engl. J. Med.* 341(21):1606-1609.
- Rajkumar et al., 2004, "Thalidomide plus dexamethasone versus dexamethasone alone in newly diagnosed multiple myeloma (E1A00): Results of a phase III trial coordinated by the Eastern Cooperative Oncology Group," *Am. Soc. Hematol.* 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract #205.
- Rajkumar et al., 2000, "Prognostic value of bone marrow angiogenesis in multiple myeloma," *Clin. Cancer Res.* 6(8):3111-3116.
- Raza et al., 2001, "Thalidomide produces transfusion independence in long-standing refractory anemias of patients with myelodysplastic syndromes," *Blood* 98(4):958-965.
- Ribatti et al., 1999, "Bone marrow angiogenesis and mast cell density increase simultaneously with progression of human multiple myeloma," *Br. J. Cancer* 79(3-4):451-455.
- Roe and Mitchley, 1963, "Thalidomide and Neoplasia" *Nature* 200:1016-1017.
- Rowland et al., 2001, "Differential effect of thalidomide and dexamethasone on the transcription factor NF- B," *Intl. Immunopharmacol.* 1:49-61.
- Rowland et al., 1999, "Selective down-regulation of T cell- and non-T cell-derived tumour necrosis factor by thalidomide: comparisons with dexamethasone," *Immunol Lett.* 68:325-332.
- Rowland et al., 1998, "Differential regulation by thalidomide and dexamethasone of cytokine expression in human peripheral blood mononuclear cells," *Immunopharmacol.* 40:11-20.
- Shah et al., 1999, "Synthesis and enantiomeric separation of 2-phthalimidino-glutaric acid analogues: potent inhibitors of tumor metastasis," *J. Med. Chem.* 42:3014-3017.
- Shibata et al., 1995, "N-alkylphthalimides: structural requirement of thalidomide action on 12-O-tetradecanoylphorbol-13-acetate-induced tumor necrosis factor production by human leukemia HL-60 cells," *Chem. Pharm. Bull.* 43(1):177-179.
- Shimazawa et al., 1999, "Antiangiogenic activity of tumor necrosis factor-alpha production regulators derived from thalidomide," *Biol. Pharm. Bull.* 22(2):224-226.
- Singhal et al., 1999, Antitumor activity of thalidomide in refractory multiple myeloma, *N. Engl. J. Med.* 341(21):1565-1571.
- Steins et al., 2002, "Efficacy and safety of thalidomide in patients with acute myeloid leukemia," *Blood* 99(3):834-839.
- Stockdale, 1998, *Medicine*, Rubenstein and Federman, eds., vol. 3, Ch. 12, Sections IV and X.
- Ural et al., 2003, "The bisphosphonate zoledronic acid induces cytotoxicity in human melanoma cell lines with enhancing effects of dexamethasone and thalidomide," *Int. J. Hematol.* 78:443-449.
- Vacca et al., 1999, "Bone marrow neovascularization, plasma cell angiogenic potential, and matrix metalloproteinase-2 secretion parallel progression of human multiple myeloma," *Blood* 93(9):3064-3073.
- Wilens et al., 1977, *Tetrahedron* 33:2725.
- Wilens, 1972, *Tables of Resolving Agents and Optical Resolutions*, E.L. Eliel, ed., Univ. of Notre Dame Press, Notre Dame, IN pp. 268.
- Wohrer et al., 2004, "Effective treatment of primary plasma cell leukemia with thalidomide and dexamethasone—a case report," *Hematol. J.* 5(4):361-363.
- Wolff ed., 1995, *Burgers's Medicinal Chemistry and Drug Discovery*, 5th ed., pp. 172-178, 949-982.
- Anderson, "Moving disease biology from the laboratory to the clinic," *Seminars in Oncology*, 2002 29:17-20.
- Barlogie et al., "Total Therapy II (TTII) for newly diagnosed multiple myeloma (MM): preliminary data on feasibility and efficacy in the first 231 enrolled patients; comparison with predecessor trial total therapy I (TTI) (N=231)," *Blood*, Abstract # 2857, Dec. 7-11, 2001, *American Society of Hematology*.
- Barlogie et al., "High-dose therapy immunomodulatory drugs in multiple myeloma," *Seminars in Oncology*, 2002, 29 (6):26-33.
- Barlogie et al., "Introduction: Thalidomide and the IMiDs in multiple myeloma," *Seminars in Hematology*, 2003, 40 (4):1-2.
- Barlogie, "Thalidomide and CC-5013 in Multiple Myeloma: The University of Arkansas experience," *Seminars in Hematology*, 2003, 40 (4):33-38.
- Bartlett et al., "The evolution of thalidomide and its IMiD derivatives as anticancer agents," *Nature Reviews Cancer*, 2004, 4 (4):1-9.
- Bartlett et al., "Phase I study to determine the safety, tolerability and immunostimulatory activity of thalidomide analogue CC-5013 in patients with metastatic malignant melanoma and other advanced cancers," *British Journal of Cancer*, 2004, 90:955-961.
- Battegay, "Angiogenesis: mechanistic insights, neovascular diseases, and therapeutic prospects," *J. Mol. Med.*, 1995, 73:333-346.
- Baz et al., "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and revlimid (R) (DVd-R) results in a high response rate in patients with refractory multiple myeloma (RMM)," *Blood*, Abstract # 2559, *American Society of Hematology*, Dec. 10-13, 2005.
- Brennen et al., "Thalidomide and analogues: current proposed mechanisms and therapeutic usage," *Clinical Prostate Cancer*, 2004, 3 (1):54-61.
- Celgene Corporation, "Celgene advances immunomodulatory drug (IMiD™) clinical program," Press Release, Feb. 2000.
- Celgene Corporation, "Initial Phase I solid tumor data on Celgene's lead IMiD™, Revimid™," Press Release, Jun. 2001.
- Celgene Corporation, "Celgene Corporation receives orphan drug designation for Revimid™ for multiple myeloma," Press Release, Oct. 2001.
- Celgene Corporation, "Celgene expands clinical development program for Revimid™. Five additional trials of Revimid initiated in hematological and solid tumor cancers," Press Release, Jun. 2002.
- Celgene Corporation, "Celgene Corporation announces third quarter results. Thalomid® (thalidomide) revenue increases 41% to \$30.5 million. Pivotal programs for Thalomid and Revimid™ finalized. Peer-reviewed publications of Thalomid and Revimid data. First JNK inhibitor advanced to Phase I clinical trial," Press Release, Oct. 2002.
- Celgene Corporation, "Blood reports Revimid™ has anti-tumor activity in patients with relapsed and refractory multiple myeloma," Press Release, Nov. 1, 2002.
- Celgene Corporation, "Celgene provides update on clinical pipeline. Celgene Announces first target indication for Actimid™, CC-8490. SelCID™ program to advance based on results from Phase I/II trial of CC-1088. First JNK inhibitor successfully completes phase I trial," Press Release, Jan. 2003.
- Celgene Corporation, "Celgene Corporation announces fourth quarter and full year results for 2002," Press Release, Jan. 2003.
- Celgene Corporation, "Celgene receives fast track status from FDA for Revimid™ in multiple myeloma," Press Release, Feb. 2003.

US 7,468,363 B2

Page 4

- Celgene Corporation, "Celgene receives fast track status from FDA for Revimid™ in myelodysplastic syndromes," Press Release, Apr. 2003.
- Celgene Corporation, "New Revimid™ clinical data shows potential as novel approach to treating myelodysplastic syndromes (MDS)," Press Release, May 2003.
- Celgene Corporation, "Celgene corporation reports strong operating performance in second quarter as total sales increase 100 percent and profits rise," Press Release, Jul. 2003.
- Celgene Corporation, "Celgene corporation reports record operating performance in third quarter as total revenue increases 117% and profits rise," Press Release, Oct. 2003.
- Celgene Corporation, "Celgene corporation advances Actimid™ (CC-4047) into phase II trial for prostate cancer," Press Release, Oct. 2003.
- Celgene Corporation, "Additional clinical data presented on Revimid™ in myelodysplastic syndromes at the American Society of Hematology 45th annual meeting," Press Release, Dec. 2003.
- Celgene Corporation, "Celgene corporation reviews 2003 achievements and announces 2004 financial outlook," Press Release, Jan. 2004.
- Celgene Corporation, "Revlimid™ receives orphan drug designation from the European commission for multiple myeloma," Press Release, Feb. 2004.
- Celgene Corporation, "Revlimid™ receives orphan drug designation from the European commission for myelodysplastic syndromes," Press Release, Mar. 2004.
- Celgene Corporation, "Celgene corporation reports record operating performance in first quarter with strong revenue growth and profits," Press Release, Apr. 2004.
- Celgene Corporation, "Celgene announces plans to stop phase III trials in melanoma due to lack of efficacy," Press Release, Apr. 2004.
- Dalgleish, et al., "New thalidomide analogues; anti-cancer, anti-angiogenic and immunostimulatory," *British Journal of Cancer*, 2001, 85 (1)25.
- Dalgleish et al., "Thalidomide analogues CC-5013 and CC-4047 induce T cell activation and IL-12 production in patients with both solid tumours and relapsed and refractory multiple myeloma," *British Journal of Cancer*, 2003, 88(Suppl 1), S25-S54.
- Davies et al., "Thalidomide (Thal) and immunomodulatory derivatives (IMiDs) augment natural killer (NK) cell cytotoxicity in multiple myeloma(MM)," Abstract # 3617, *American Society of Hematology*, Dec. 1-5, 2000.
- Davies et al., "Thalidomide (Thal) and immunomodulatory derivatives (IMiDs) augment natural killer (NK) cell cytotoxicity in multiple myeloma ~MM)," Abstract # P222, *VIIIth International Myeloma Workshop*, May 4-8, 2001.
- Dibbs et al., "Thalidomide and thalidomide analogs suppress TNF α secretion by myocytes," Abstract # 1284, *Circulation*, 1998.
- Dimopoulos et al., "Results of thalidomide and IMiDs in multiple myeloma," Abstract # P12.1.4, *International Multiple Myeloma Workshop*, May 23-27, 2003.
- Dimopoulos et al., "Treatment of plasma cell dyscrasias with thalidomide and its derivatives," *Journal of Clinical Oncology*, Dec. 1, 2003, 21 (23)4444-4454.
- Dimopoulos et al., "Study of lenalidomide plus dexamethasone versus dexamethasone alone in relapsed or refractory multiple myeloma (MM): Results of a phase 3 Study (MM-010)," Abstract # 6, *American Society of Hematology*, Dec. 10-13, 2005.
- Dredge et al., "A costimulatory thalidomide analog enhances the partial anti-tumor immunity of an autologous vaccination in a model of colorectal cancer," Abstract # 491, *American Association for Cancer Research*, Apr. 6-10, 2002.
- Dredge et al., "Adjuvants and the promotion of Th1-type cytokines in tumour immunotherapy," *Cancer Immunol. Immunother.*, 2002, 51:521-531.
- Dredge et al., "Immunological effects of thalidomide and its chemical and functional analogs," *Critical Reviews in Immunology*, 2002, 22 (5&6):425-437.
- Dredge et al., "Protective antitumor immunity induced by a costimulatory thalidomide analog in conjunction with whole tumor cell vaccination is mediated by increased Th1-type immunity¹," *The Journal of Immunology*, 2002, 168:4914-4919.
- Dredge et al., "Recent developments in antiangiogenic therapy," *Expert Opin. Biol. Ther.*, 2002, 2 (8):953-966.
- Dredge et al., "Angiogenesis inhibitors in cancer therapy," *Current Opinion in Investigational Drugs*, 2003, 4 (6):667-674.
- Dredge et al., "Thalidomide analogs as emerging anti-cancer drugs," *Anti-Cancer Drugs*, 2003, 14:331-335.
- Fickentscher et al., "Stereochemical properties and teratogenic activity of some tetrahydrophthalimides," *Molecular Pharmacology*, 1976, 13:133-141.
- Galustian et al., "Thalidomide-derived immunomodulatory drugs as therapeutic agents," *Expert Opin. Biol. Ther.*, 2004, 4 (12):1-8.
- Glaspy et al., "The potential role of thalidomide and thalidomide analogs in melanoma," *Clinical Advances on Hematology & Oncology*, 2004, 1-7.
- Hayashi et al., "Mechanisms whereby immunomodulatory analogs of thalidomide augment autologous NK cell anti-myeloma immunity," *Blood*, Abstract #3219, Dec. 6-10, 2002, *American Society of Hematology*.
- Helm et al., "Comparative teratological investigation of compounds of structurally and pharmacologically related to thalidomide," *Arzneimittel Forschung/Drug Research*, 1981, 31 (I)941-949.
- Hernandez-Illizaliturri et al., "Addition of immunomodulatory drugs CC5013 or CC4047 to rituximab enhances anti-tumor activity in a severe combined immunodeficiency (SCID) mouse lymphoma model," Abstract # 235, *American Society of Hematology*, Dec. 6-9, 2003.
- Hideshima et al., "Thalidomide (Thal) and its analogs overcome drug resistance of human multiple myeloma (MM) cells to conventional therapy," Abstract 1313, *American Society of Hematology*, Dec. 1-5, 2000.
- Hunt et al., "Markers of endothelial and haemostatic activation in the use of CC-4047, a structural analogue of thalidamide, in relapsed myeloma," *Blood*, Abstract # 3216, Dec. 6-10, 2002, *American Society of Hematology*.
- Hussein et al., "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and Revlimid (DvD-R) a phase I/II trial in advanced relapsed/refractory multiple myeloma (Rmm) patients," *Blood*, Abstract #208, *American Society of Hematology*, Dec. 4-7, 2004.
- Hwu et al., "Thalidomide and its analogues in the treatment of metastatic melanoma," *Chemotherapy Foundation Symposium*, Abstract #44, 2002.
- Kyle, "Current therapy of multiple myeloma," *Internal Medicine*, 2002, 41 (3)175-180.
- Kyle et al., "Multiple myeloma," *New England Journal of Medicine*, 2004, 351:1860-1873.
- Leblanc et al., "Immunomodulatory drug costimulates T cells via the B7-CD28 pathway," *Blood*, 2004, 103:1787-1790, *American Society of Hematology*.
- Lentzsch et al., "In vivo activity of thalidomide and immunomodulatory drugs against multiple myeloma," *VIIIth International Myeloma Workshop*, Abstract #P225, May 4-8, 2001.
- Lentzsch et al., "Immunomodulatory derivative of thalidomide (IMiD CC-4047) determine the lineage commitment of hematopoietic progenitors by down regulation of GATA-1 and modulation of cytokine secretion," Abstract # 3073, *American Society of Hematology*, Dec. 6-9, 2003.
- Lentzsch et al., "Immunomodulatory derivative of thalidomide (IMiD CC-4047) down regulates CAAT/enhancer-binding protein β (C/EBP β) in multiple myeloma (MM)," Abstract# 3456, *American Society of Hematology*, Dec. 6-9, 2003.
- Luzzio et al., "Thalidomide analogues: derivatives of an orphan drug with diverse biological activity," *Expert Opin. Ther. Patents*, 2004, 14 (2):215-229.
- Man et al., " α -Fluoro-substituted thalidomide analogues," *Bioorganic & Medicinal Chemistry Letters* 13, 2003, 3415-3417.
- Marriott et al., "Immunotherapeutic and antitumour potential of thalidomide analogues," *Expert Opin. Biol. Ther.*, 2001, 1 (4):1-8.
- Marriott et al., "New thalidomide analogues; anti-cancer, anti-angiogenic and immunostimulatory," *British Journal of Cancer*, 85:25, Jul. 6, 2001.

US 7,468,363 B2

Page 5

- Marriott et al., "Thalidomide and its analogues have distinct and opposing effects on TNF- α and TNFR2 during co-stimulation of both CD4⁺ and CD8⁺ T cells," *Clin. Exp. Immunol.*, 2002, 130:75-84.
- Marriott et al., "A novel subclass of thalidomide analogue with anti-solid tumor activity in which caspase-dependent apoptosis is associated with altered expression of bcl-2 family proteins¹," *Cancer Research*, 2003, 63:593-599.
- Marriott et al., "Thalidomide derived immunomodulatory drugs (IMiDs) as potential therapeutic agents," *Current Drug Targets—Immune, Endocrine & Metabolic Disorders*, 2003, 3:181-186.
- Masellis et al., "Changes in gene expression in bone marrow mesenchymal progenitor cells as a consequence of IMiD therapy in multiple myeloma patients," *Blood*, Abstract # 1548, Dec. 7-11, 2001, *American Society of Hematology*.
- McCarty, "Thalidomide may impede cell migration in primates by down-regulating integrin β -chains: potential therapeutic utility in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis," *Medical Hypotheses*, 1997, 49:123-131.
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs (ImiDs) in human multiple myeloma cells: therapeutic implications," Abstract # 3224, Dec. 7-11, 2001, *American Society of Hematology*.
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications," *Blood*, 2002, 99:4525-4530, *American Society of Hematology*.
- Mitsiades et al., "CC-5013 Celgene," *Current Opinion in Investigational Drugs*, 2004, 5 (6):635-647.
- Moutouh et al., "Novel immunomodulatory drugs (IMiD®): A potential, new therapy for β -hemoglobinopathies," Abstract # 3740, *American Society of Hematology*, Dec. 4-7, 2004.
- Patten et al., "The early use of the serum free light chain assay in patients with relapsed refractory myeloma receiving treatment with a thalidomide analogue (CC-4047)," Abstract # 1640, *American Society of Hematology*, Dec. 6-9, 2003.
- Payvandi et al., "Effects of a thalidomide analog on binding activity of transcription factors and cell cycle progression of multiple myeloma cell lines," *Blood*, Abstract #2487, Dec. 1-5, 2000, *American Society of Hematology*.
- Payvandi et al., "The thalidomide analogs IMiDs enhance expression of CD69 stimulatory receptor on natural killer cells," Abstract # 1793, *American Association for Cancer Research*, Mar. 24-28, 2001.
- Payvandi et al., "Thalidomide analogs IMiDs inhibit expression of cyclooxygenase-2 in multiple myeloma cell line and LPS stimulated PBMCs," *Blood*, Abstract # 2689, Dec. 7-11, 2001, *American Society of Hematology*.
- Payvandi et al., "Thalidomide and IMiDs inhibit microvessel formation from human arterial rings in the absence of human liver microsomes," *Blood*, Abstract # 5046, Dec. 6-10, 2002, *American Society of Hematology*.
- Payvandi et al., "CC-5013 inhibits the expression of adhesion molecules ICAM-1 and CD44 and prevents metastasis of B16 F10 mouse melanoma cells in an animal model," *American Society of Clinical Oncology*, Abstract # 992, 2003.
- Payvandi et al., "Immunomodulatory drugs inhibit expression of cyclooxygenase-2 from TNF- α , IL- β , and LPS-stimulated human PBMC in a partially IL-10-dependent manner," *Cellular Immunology*, 2004, 81-88.
- Raje et al., "Combination of the mTOR inhibitor rapamycin and CC-5013 has synergistic activity in multiple myeloma," *Blood*, Dec. 15, 2004, 104 (13):4188-4193.
- Rajkumar et al., "Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma," *Blood*, Dec. 15, 2005, 106 (13):4050-4053.
- Richardson et al., "A Phase I study of oral CC5013, an immunomodulatory thalidomide (Thal) derivative, in patients with relapsed and refractory multiple myeloma (MM)," *Blood*, Abstract #3225, Dec. 7-11, 2001, *American Society of Hematology*.
- Richardson et al., "Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma," *Blood*, 2002 100:3063-3067, *American Society of Hematology*.
- Richardson et al., "A multi-center, randomized, phase 2 study to evaluate the efficacy and safety of 2 CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM)," *Blood*, Abstract # 825, *American Society of Hematology*, Dec. 6-9, 2003.
- Richardson et al., "Immunomodulatory analogs of thalidomide: an emerging new therapy in myeloma," *Journal of Clinical Oncology*, 2004, 22(16):3212-3214.
- Richardson et al., "A multicenter, single-arm, open-label study to evaluate the efficacy and safety of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma; preliminary results," 10th *International Myeloma Workshop*, Apr. 10-14, 2005.
- Richardson et al., "Novel biological therapies for the treatment of multiple myeloma," *Best Practice & Research Clinical Haematology*, 2005, 18 (4):619-634.
- Richardson et al., "A phase I trial of lenalidomide (Revlimid®) with bortezomib (Velcade®) in relapsed and refractory multiple myeloma," *Blood*, Abstract # 365, *American Society of Hematology*, Dec. 10-13, 2005.
- Rubin et al., "Principles of cancer treatment-1," 2003, 12 *Onco IV* 1.
- Schafer et al., "Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs," *Journal of Pharmacology and Experimental Therapeutics*, 2003, 305(3):1222-1232.
- Schey et al., "A phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma," *Journal of Clinical Oncology*, 2004, 22 (16):1-8.
- Schey et al., "A phase I study of an immunomodulatory thalidomide analogue (CC4047) in relapse/refractory multiple myeloma," *International Society for Experimental Hematology*, Abstract #248, 2002.
- Shaughnessy et al., "Global gene expression analysis shows loss of C-MYC and IL-6 receptor gene mRNA after exposure of myeloma to thalidomide and IMiD," Abstract # 2485, *The American Society of Hematology*, Dec. 1-5, 2000.
- Shire et al., "TNF- α inhibitors and rheumatoid arthritis," *Exp. Opin. Ther. Patents*, 1998, 8 (5):531-544.
- Sorbera et al., "CC-5013. Treatment of multiple myeloma. Treatment of Melanoma. Treatment of myelodysplastic syndrome. Angiogenesis inhibitor. TNF- α production inhibitor," *Drugs of the Future*, 2003, 28(5):425-431.
- Streety et al., "Thalidomide analogue CC-4047 is effective in the treatment of patients with relapsed and refractory multiple myeloma (MM) and induces T-cell activation and IL-12 production," Abstract # 367, *International Multiple Myeloma Workshop*, May 23-27, 2003.
- Streety et al., "Changes in neutrophil phenotype following the administration of CC-4047 (Actimid) to patients with multiple myeloma," Abstract # 2543, *American Society of Hematology*, Dec. 6-9, 2003.
- Streety et al., "An update of the use and outcomes of the new immunomodulatory agent CC-4047 (Actimid) in patients with relapsed/refractory myeloma," Abstract #829, *American Society of Hematology*, Dec. 6-9, 2003.
- Teo et al., "A phase I, single-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacokinetic study of CDC-501, a novel immunomodulatory- oncologic agent, in healthy male subjects with a comparison of fed and fasted," *Clinical Pharmacology and Therapeutics*, 2002, 71 (2):93.
- Teo et al., "Chiral inversion of the second generation IMiD™ CC-4047 (Actimid™) in human plasma and phosphate-buffered saline," *Chirality*, 2003, 15:348-351.
- Thertulien et al., "Hybrid MEL/DT PACE autotransplant regimen for Multiple Myeloma (MM)- safety and efficacy data in pilot study of 15 patients," *Blood*, Abstract # 2869, *American Society of Hematology*, Dec. 7-11, 2001.
- Tohny et al., "A phase I study of oral CC-5013 (lenalidomide, Revlimid™), a thalidomide derivative, in patients with refractory metastatic cancer," *Clinical Prostate Cancer*, 2004, 2:241-243.
- Tricot et al., "Angiochemotherapy (ACT) for multiple myeloma (MM) with DT-PACE results in a high response rate, but in contrast to

US 7,468,363 B2

Page 6

tandem transplants with melphalan does not affect durable disease control," *Blood*, Abstract # 3531, *American Society of Hematology*, Dec. 7-11, 2001.

Tsenova et al., "Use of IMiD3, a thalidomide analog, as an adjunct to therapy for experimental tuberculous meningitis," *Antimicrobial Agents and Chemotherapy*, 2002, 46 (6)1887-1895.

Weber, "Lenalidomide (CC-5013, Revlimid™) and other ImiDs," Abstract # PL5.02, *International Multiple Myeloma Workshop*, Apr. 10-14, 2005.

Weber et al., "A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma," Abstract #PO.738, *International Multiple Myeloma Workshop*, Apr. 10-14, 2005.

Ye et al., "Novel IMiD drugs enhance expansion and regulate differentiation of human cord blood CD34+ cells with cytokines," *Blood*, Abstract #4099, *American Society of Hematology*, Dec. 6-10, 2002.

Zangari et al., "Risk factors for deep vein thrombosis (DVT) in a large group of myeloma patients (Pts) treated with thalidomide (Thal): The Arkansas Experience," *Blood*, Abstract # 681, *American Society of Hematology*, Dec. 7-11, 2001.

Zangari et al., "Revimid 25 mg (REV 25)×20 versus 50 mg (REV 50)×10 q 28 days with bridging of 5 mg×10 versus 10 mg×5 as post-transplant salvage therapy for multiple myeloma (MM)," *Blood*, Abstract # 1642, *American Society of Hematology*, Dec. 6-9, 2003.

Zeldis et al., "Potential new therapeutics for Waldenstrom's macroglobulinemia," *Seminars in Oncology*, 2003, 30 (2):275-281.

Zhang et al., "CC-5079, a novel microtubule and TNF-α inhibitor with anti-angiogenic and antimetastasis activity," Abstract # B012, *International Conference on Molecular Targets and Cancer Therapeutics*, Nov. 17-21, 2003.

Lie et al., "Phase I study of CC-5013 (Revimid), a thalidomide derivative, in patients with refractory metastatic cancer," *American Society of Clinical Oncology*, Abstract #927, 2003.

Zangari et al., "Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (HDCT)," *American Society of Hematology*, Abstract #3226, 2001.

Zeldis et al., "Update on the evolution of the IMiD™," *International Society of Biological Therapy of Cancer*, Oral Abstract, 2003.

Dispenzieri, et al., "Cardiac biomarkers predict for ability to tolerate and complete therapy with lenalidomide±dexamethasone in AL amyloidosis," *Amer. Soc. of Hematology*, Abstract #130, Dec. 2006.

Witzig, et al., "Results from a phase II study of lenalidomide oral monotherapy in relapsed/refractory indolent non-Hodgkin's lymphoma," *Amer. Soc. of Hematology*, Abstract #2560, Dec. 2007.

Seldin, et al., "Durable responses to lenalidomide (Revlimid®) in patients with AL amyloidosis: Follow up of a phase II trial," *Amer. Soc. of Hematology*, Abstract #192, Dec. 2007.

Querfeld, et al., "Lenalidomide in patients with cutaneous T-cell lymphoma: Preliminary data of phase II trial," *The Society of Investigative Dermatology*, Abstract #270, May 2006.

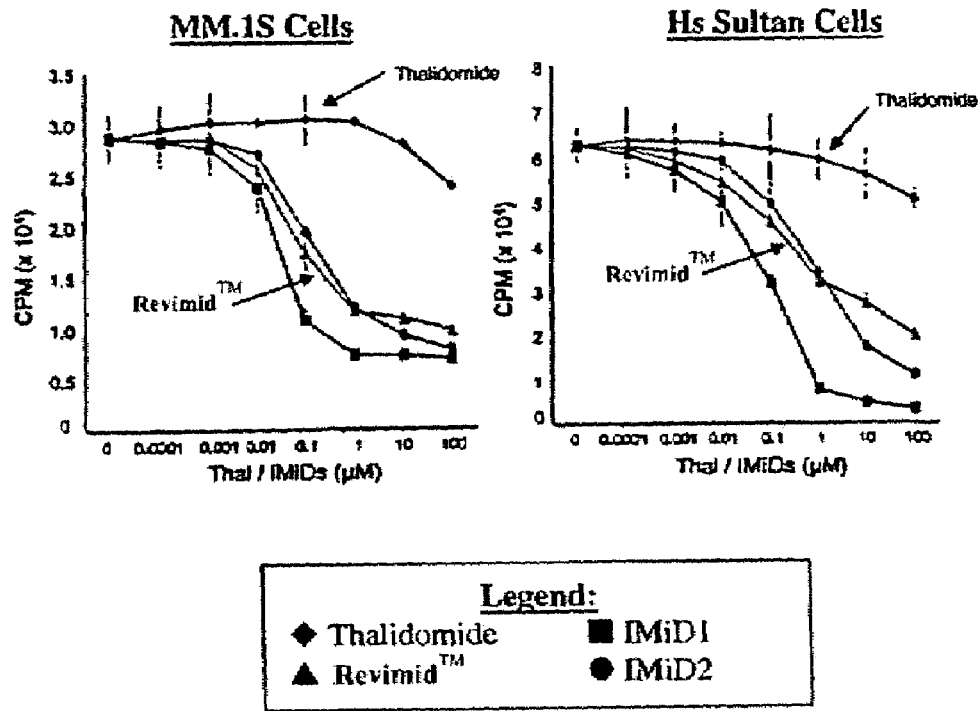
Lossos, et al., "Lenalidomide response in relapsed/refractory diffuse large B-cell non-Hodgkin's lymphoma," *Amer. Soc. of Hematology*, Abstract #2564, Dec. 2007.

Santhorawala, et al., "Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial," *Blood*, Jan. 2007, 109(2):492-496.

Zhang et al., "Safety and efficacy of lenalidomide (Revlimid®) in recurrent ovarian and primary peritoneal carcinoma," *Gynecologic Oncology*, 2007, 105:194-198.

* cited by examiner

Figure 1
Effects of Revimid™ and Thalidomide on MM Cell Proliferation



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METHODS FOR TREATMENT OF CANCERS USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL- 2-YL)-PIPERIDINE-2,6-DIONE

CROSS-REFERENCE TO RELATED APPLICATION

This application is a divisional application of U.S. patent application Ser. No. 10/438,213, filed May 15, 2003, presently pending, which claims the benefit of U.S. provisional application Nos. 60/380,842, filed May 17, 2002, and 60/424,600, filed Nov. 6, 2002, the entireties of which are incorporated herein by reference.

1. FIELD OF THE INVENTION

This invention relates to methods of treating, preventing and/or managing specific cancers, and other diseases including, but not limited to, those associated with, or characterized by, undesired angiogenesis, by the administration of one or more immunomodulatory compounds alone or in combination with other therapeutics. In particular, the invention encompasses the use of specific combinations, or "cocktails," of drugs and other therapy, e.g., radiation to treat these specific cancers, including those refractory to conventional therapy. The invention also relates to pharmaceutical compositions and dosing regimens.

2. BACKGROUND OF THE INVENTION

2.1 Pathobiology of Cancer and Other Diseases

Cancer is characterized primarily by an increase in the number of abnormal cells derived from a given normal tissue, invasion of adjacent tissues by these abnormal cells, or lymphatic or blood-borne spread of malignant cells to regional lymph nodes and to distant sites (metastasis). Clinical data and molecular biologic studies indicate that cancer is a multistep process that begins with minor preneoplastic changes, which may under certain conditions progress to neoplasia. The neoplastic lesion may evolve clonally and develop an increasing capacity for invasion, growth, metastasis, and heterogeneity, especially under conditions in which the neoplastic cells escape the host's immune surveillance. Roitt, I., Brostoff, J and Kale, D., *Immunology*, 17.1-17.12 (3rd ed., Mosby, St. Louis, Mo., 1993).

There is an enormous variety of cancers which are described in detail in the medical literature. Examples includes cancer of the lung, colon, rectum, prostate, breast, brain, and intestine. The incidence of cancer continues to climb as the general population ages, as new cancers develop, and as susceptible populations (e.g., people infected with AIDS or excessively exposed to sunlight) grow. A tremendous demand therefore exists for new methods and compositions that can be used to treat patients with cancer.

Many types of cancers are associated with new blood vessel formation, a process known as angiogenesis. Several of the mechanisms involved in tumor-induced angiogenesis have been elucidated. The most direct of these mechanisms is the secretion by the tumor cells of cytokines with angiogenic properties. Examples of these cytokines include acidic and basic fibroblastic growth factor (a,b-FGF), angiogenin, vascular endothelial growth factor (VEGF), and TNF- α . Alternatively, tumor cells can release angiogenic peptides through the production of proteases and the subsequent breakdown of the extracellular matrix where some cytokines are stored (e.g., b-FGF). Angiogenesis can also be induced indirectly

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through the recruitment of inflammatory cells (particularly macrophages) and their subsequent release of angiogenic cytokines (e.g., TNF- α , bFGF).

A variety of other diseases and disorders are also associated with, or characterized by, undesired angiogenesis. For example, enhanced or unregulated angiogenesis has been implicated in a number of diseases and medical conditions including, but not limited to, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, rubeosis (neovascularization of the angle), viral diseases, genetic diseases, inflammatory diseases, allergic diseases, and autoimmune diseases. Examples of such diseases and conditions include, but are not limited to: diabetic retinopathy; retinopathy of prematurity; corneal graft rejection; neovascular glaucoma; retrolental fibroplasia; and proliferative vitreoretinopathy.

Accordingly, compounds that can control angiogenesis or inhibit the production of certain cytokines, including TNF- α , may be useful in the treatment and prevention of various diseases and conditions.

2.2 Methods of Treating Cancer

Current cancer therapy may involve surgery, chemotherapy, hormonal therapy and/or radiation treatment to eradicate neoplastic cells in a patient (see, for example, Stockdale, 1998, *Medicine*, vol. 3, Rubenstein and Federman, eds., Chapter 12, Section IV). Recently, cancer therapy could also involve biological therapy or immunotherapy. All of these approaches pose significant drawbacks for the patient. Surgery, for example, may be contraindicated due to the health of a patient or may be unacceptable to the patient. Additionally, surgery may not completely remove neoplastic tissue. Radiation therapy is only effective when the neoplastic tissue exhibits a higher sensitivity to radiation than normal tissue. Radiation therapy can also often elicit serious side effects. Hormonal therapy is rarely given as a single agent. Although hormonal therapy can be effective, it is often used to prevent or delay recurrence of cancer after other treatments have removed the majority of cancer cells. Biological therapies and immunotherapies are limited in number and may produce side effects such as rashes or swellings, flu-like symptoms, including fever, chills and fatigue, digestive tract problems or allergic reactions.

With respect to chemotherapy, there are a variety of chemotherapeutic agents available for treatment of cancer. A majority of cancer chemotherapeutics act by inhibiting DNA synthesis, either directly, or indirectly by inhibiting the biosynthesis of deoxyribonucleotide triphosphate precursors, to prevent DNA replication and concomitant cell division. Gilman et al., *Goodman and Gilman's: The Pharmacological Basis of Therapeutics*, Tenth Ed. (McGraw Hill, New York).

Despite availability of a variety of chemotherapeutic agents, chemotherapy has many drawbacks. Stockdale, *Medicine*, vol. 3, Rubenstein and Federman, eds., ch. 12, sect. 10, 1998. Almost all chemotherapeutic agents are toxic, and chemotherapy causes significant, and often dangerous side effects including severe nausea, bone marrow depression, and immunosuppression. Additionally, even with administration of combinations of chemotherapeutic agents, many tumor cells are resistant or develop resistance to the chemotherapeutic agents. In fact, those cells resistant to the particular chemotherapeutic agents used in the treatment protocol often prove to be resistant to other drugs, even if those agents act by different mechanism from those of the drugs used in the specific treatment. This phenomenon is referred to as pleio-

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tropic drug or multidrug resistance. Because of the drug resistance, many cancers prove refractory to standard chemotherapeutic treatment protocols.

Other diseases or conditions associated with, or characterized by, undesired angiogenesis are also difficult to treat. However, some compounds such as protamine, heparin and steroids have been proposed to be useful in the treatment of certain specific diseases. Taylor et al., *Nature* 297:307 (1982); Folkman et al., *Science* 221:719 (1983); and U.S. Pat. Nos. 5,001,116 and 4,994,443. Thalidomide and certain derivatives of it have also been proposed for the treatment of such diseases and conditions. U.S. Pat. Nos. 5,593,990, 5,629,327, 5,712,291, 6,071,948 and 6,114,355 to D'Amato.

Still, there is a significant need for safe and effective methods of treating, preventing and managing cancer and other diseases and conditions, particularly for diseases that are refractory to standard treatments, such as surgery, radiation therapy, chemotherapy and hormonal therapy, while reducing or avoiding the toxicities and/or side effects associated with the conventional therapies.

2.3 IMiDs™

A number of studies have been conducted with the aim of providing compounds that can safely and effectively be used to treat diseases associated with abnormal production of TNF- α . See, e.g., Marriott, J. B., et al., *Expert Opin. Biol. Ther.* 1(4):1-8 (2001); G. W. Muller, et al., *Journal of Medicinal Chemistry* 39(17):3238-3240 (1996); and G. W. Muller, et al., *Bioorganic & Medicinal Chemistry Letters* 8: 2669-2674 (1998). Some studies have focused on a group of compounds selected for their capacity to potentially inhibit TNF- α production by LPS stimulated PBMC. L. G. Corral, et al., *Ann. Rheum. Dis.* 58:(Suppl 1) 1107-1113 (1999). These compounds, which are referred to as IMiDs™ (Celgene Corporation) or Immunomodulatory Drugs, show not only potent inhibition of TNF- α but also marked inhibition of LPS induced monocyte IL1 β and IL12 production. LPS induced IL6 is also inhibited by immunomodulatory compounds, albeit partially. These compounds are potent stimulators of LPS induced IL10. Id. Particular examples of IMiDs™ include, but are not limited to, the substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoles described in U.S. Pat. Nos. 6,281,230 and 6,316,471, both to G. W. Muller, et al.

3. SUMMARY OF THE INVENTION

This invention encompasses methods of treating and preventing certain types of cancer, including primary and metastatic cancer, as well as cancers that are refractory or resistant to conventional chemotherapy. The methods comprise administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. The invention also encompasses methods of managing certain cancers (e.g., preventing or prolonging their recurrence, or lengthening the time of remission) which comprise administering to a patient in need of such management a prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

In particular methods of the invention, an immunomodulatory compound is administered in combination with a therapy conventionally used to treat, prevent or manage can-

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cer. Examples of such conventional therapies include, but are not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy.

This invention also encompasses methods of treating, managing or preventing diseases and disorders other than cancer that are associated with, or characterized by, undesired angiogenesis, which comprise administering to a patient in need of such treatment, management or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

In other methods of the invention, an immunomodulatory compound is administered in combination with a therapy conventionally used to treat, prevent or manage diseases or disorders associated with, or characterized by, undesired angiogenesis. Examples of such conventional therapies include, but are not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy.

This invention encompasses pharmaceutical compositions, single unit dosage forms, dosing regimens and kits which comprise an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a second, or additional, active agent. Second active agents include specific combinations, or "cocktails," of drugs.

4. BRIEF DESCRIPTION OF FIGURE

FIG. 1 shows a comparison of the effects of 3-(4-amino-1-oxo-1,3-dihydro-isindol-2-yl)-piperidine-2,6-dione (Revimid™) and thalidomide in inhibiting the proliferation of multiple myeloma (MM) cell lines in an in vitro study. The uptake of [³H]-thymidine by different MM cell lines (MM.1S, Hs Sultan, U266 and RPMI-8226) was measured as an indicator of the cell proliferation.

5. DETAILED DESCRIPTION OF THE INVENTION

A first embodiment of the invention encompasses methods of treating, managing, or preventing cancer which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

In particular methods encompassed by this embodiment, the immunomodulatory compound is administered in combination with another drug ("second active agent") or method of treating, managing, or preventing cancer. Second active agents include small molecules and large molecules (e.g., proteins and antibodies), examples of which are provided herein, as well as stem cells. Methods, or therapies, that can be used in combination with the administration of the immunomodulatory compound include, but are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation therapy, and other non-drug based therapies presently used to treat, prevent or manage cancer.

Another embodiment of the invention encompasses methods of treating, managing or preventing diseases and disorders other than cancer that are characterized by undesired angiogenesis. These methods comprise the administration of a therapeutically or prophylactically effective amount of an immunomodulatory compound, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof.

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Examples of diseases and disorders associated with, or characterized by, undesired angiogenesis include, but are not limited to, inflammatory diseases, autoimmune diseases, viral diseases, genetic diseases, allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular diseases, retina neovascular diseases, and rubeosis (neovascularization of the angle).

In particular methods encompassed by this embodiment, the immunomodulatory compound is administered in combination with a second active agent or method of treating, managing, or preventing the disease or condition. Second active agents include small molecules and large molecules (e.g., proteins and antibodies), examples of which are provided herein, as well as stem cells. Methods, or therapies, that can be used in combination with the administration of the immunomodulatory compound include, but are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation therapy, and other non-drug based therapies presently used to treat, prevent or manage disease and conditions associated with, or characterized by, undesired angiogenesis.

The invention also encompasses pharmaceutical compositions (e.g., single unit dosage forms) that can be used in methods disclosed herein. Particular pharmaceutical compositions comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, and a second active agent.

5.1 Immunomodulatory Compounds

Compounds used in the invention include immunomodulatory compounds that are racemic, stereomerically enriched or stereomerically pure, and pharmaceutically acceptable salts, solvates, hydrates, stereoisomers, clathrates, and prodrugs thereof. Preferred compounds used in the invention are small organic molecules having a molecular weight less than about 1,000 g/mol, and are not proteins, peptides, oligonucleotides, oligosaccharides or other macromolecules.

As used herein and unless otherwise indicated, the terms "immunomodulatory compounds" and "IMiDs™" (Celgene Corporation) encompasses small organic molecules that markedly inhibit TNF- α , LPS induced monocyte IL1 β and IL12, and partially inhibit IL6 production. Specific immunomodulatory compounds are discussed below.

TNF- α is an inflammatory cytokine produced by macrophages and monocytes during acute inflammation. TNF- α is responsible for a diverse range of signaling events within cells. TNF- α may play a pathological role in cancer. Without being limited by theory, one of the biological effects exerted by the immunomodulatory compounds of the invention is the reduction of synthesis of TNF- α . Immunomodulatory compounds of the invention enhance the degradation of TNF- α mRNA.

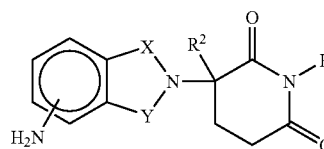
Further, without being limited by theory, immunomodulatory compounds used in the invention may also be potent co-stimulators of T cells and increase cell proliferation dramatically in a dose dependent manner. Immunomodulatory compounds of the invention may also have a greater co-stimulatory effect on the CD8+ T cell subset than on the CD4+ T cell subset. In addition, the compounds preferably have anti-inflammatory properties, and efficiently co-stimulate T cells.

Specific examples of immunomodulatory compounds of the invention, include, but are not limited to, cyano and carboxy derivatives of substituted styrenes such as those disclosed in U.S. Pat. No. 5,929,117; 1-oxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl) isoindolines and 1,3-dioxo-2-(2,6-

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dioxo-3-fluoropiperidine-3-yl) isoindolines such as those described in U.S. Pat. No. 5,874,448; the tetra substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolines described in U.S. Pat. No. 5,798,368; 1-oxo and 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines (e.g., 4-methyl derivatives of thalidomide and EM-12), including, but not limited to, those disclosed in U.S. Pat. No. 5,635,517; and a class of non-polypeptide cyclic amides disclosed in U.S. Pat. Nos. 5,698,579 and 5,877,200; analogs and derivatives of thalidomide, including hydrolysis products, metabolites, derivatives and precursors of thalidomide, such as those described in U.S. Pat. Nos. 5,593,990, 5,629,327, and 6,071,948 to D'Amato; aminothalidomide, as well as analogs, hydrolysis products, metabolites, derivatives and precursors of aminothalidomide, and substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoles such as those described in U.S. Pat. Nos. 6,281,230 and 6,316,471; isoindole-imide compounds such as those described in U.S. patent application Ser. No. 09/972,487 filed on Oct. 5, 2001, U.S. patent application Ser. No. 10/032,286 filed on Dec. 21, 2001, and International Application No. PCT/US01/50401 (International Publication No. WO 02/059106). The entireties of each of the patents and patent applications identified herein are incorporated herein by reference. Immunomodulatory compounds of the invention do not include thalidomide.

Other specific immunomodulatory compounds of the invention include, but are not limited to, 1-oxo- and 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl) isoindolines substituted with amino in the benzo ring as described in U.S. Pat. No. 5,635,517 which is incorporated herein by reference. These compounds have the structure 1:



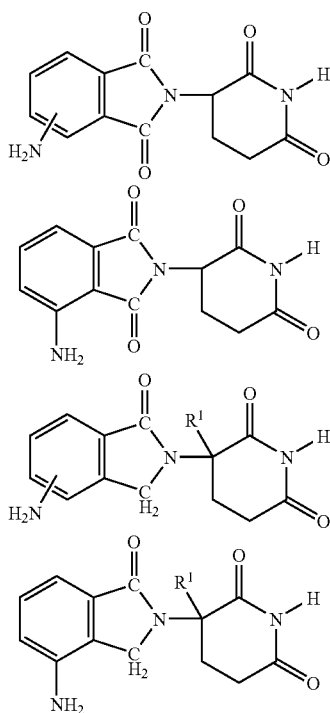
in which one of X and Y is C=O, the other of X and Y is C=O or CH₂, and R² is hydrogen or lower alkyl, in particular methyl. Specific immunomodulatory compounds include, but are not limited to:

- 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline;
- 1-oxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline;
- 1-oxo-2-(2,6-dioxopiperidin-3-yl)-6-aminoisoindoline;
- 1-oxo-2-(2,6-dioxopiperidin-3-yl)-7-aminoisoindoline;
- 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline;
- and
- 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline.

Other specific immunomodulatory compounds of the invention belong to a class of substituted 2-(2,6-dioxopiperidin-3-yl) phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisindoles, such as those described in U.S. Pat. Nos. 6,281,230; 6,316,471; 6,335,349; and 6,476,052, and International Patent Application No. PCT/US97/13375 (International Publication No. WO 98/03502), each of which is incorporated herein by reference. Compounds representative of this class are of the formulas:

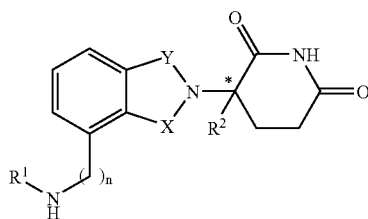
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wherein R^1 is hydrogen or methyl. In a separate embodiment, the invention encompasses the use of enantiomerically pure forms (e.g. optically pure (R) or (S) enantiomers) of these compounds.

Still other specific immunomodulatory compounds of the invention belong to a class of isoindole-imides disclosed in U.S. patent application Ser. Nos. 10/032,286 and 09/972,487, and International Application No. PCT/US01/50401 (International Publication No. WO 02/059106), each of which are incorporated herein by reference. Representative compounds are of formula II:



and pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, and mixtures of stereoisomers thereof, wherein:

one of X and Y is $C=O$ and the other is CH_2 or $C=O$;

R^1 is H, (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl- C_1-C_6 heterocycloalkyl, (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, $C(O)R^3$, $C(S)R^3$, $C(O)OR^4$, (C_1-C_8) alkyl- $N(R^6)_2$, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl- $C(O)OR^5$, $C(O)NHR^3$, $C(S)NHR^3$, $C(O)NR^3R^3$, $C(S)NR^3R^3$ or (C_1-C_8) alkyl- $O(CO)R^5$;

R^2 is H, F, benzyl, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, or (C_2-C_8) alkynyl;

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R^3 and $R^{3'}$ are independently (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, (C_0-C_8) alkyl- $N(R^6)_2$, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl- $(O)OR^5$, (C_1-C_8) alkyl- $O(CO)R^5$, or $C(O)OR^5$;

R^4 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_1-C_4) alkyl- OR^5 , benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, or (C_0-C_4) alkyl- (C_2-C_5) heteroaryl;

R^5 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, or (C_2-C_5) heteroaryl;

each occurrence of R^6 is independently H, (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_2-C_5) heteroaryl, or (C_0-C_8) alkyl- $C(O)O-R^5$ or the R^6 groups can join to form a heterocycloalkyl group;

n is 0 or 1; and

* represents a chiral-carbon center.

In specific compounds of formula II, when n is 0 then R^1 is (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl- C_1-C_6 heterocycloalkyl, (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, $C(O)R^3$, $C(O)OR^4$, (C_1-C_8) alkyl- $N(R^6)_2$, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl- $C(O)OR^5$, $C(S)NHR^3$, or (C_1-C_8) alkyl- $O(CO)R^5$;

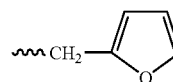
R^2 is H or (C_1-C_8) alkyl; and

R^3 is (C_1-C_8) alkyl, (C_3-C_7) cycloalkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, benzyl, aryl, (C_0-C_4) alkyl- (C_1-C_6) heterocycloalkyl, (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, (C_5-C_8) alkyl- $N(R^6)_2$, (C_0-C_8) alkyl- $NH-C(O)O-R^5$, (C_1-C_8) alkyl- OR^5 , (C_1-C_8) alkyl- $C(O)OR^5$, (C_1-C_8) alkyl- $O(CO)R^5$, or $C(O)OR^5$; and the other variables have the same definitions.

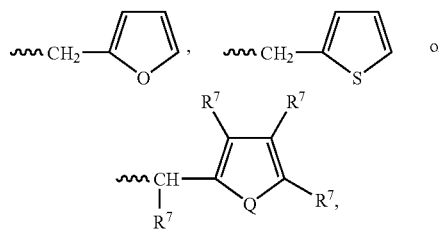
In other specific compounds of formula II, R^2 is H or (C_1-C_4) alkyl.

In other specific compounds of formula II, R^1 is (C_1-C_8) alkyl or benzyl.

In other specific compounds of formula II, R^1 is H, (C_1-C_8) alkyl, benzyl, CH_2OCH_3 , $CH_2CH_2OCH_3$, or



In another embodiment of the compounds of formula II, R^1 is



wherein Q is O or S, and each occurrence of R^7 is independently H, (C_1-C_8) alkyl, benzyl, CH_2OCH_3 , or $CH_2CH_2OCH_3$.

In other specific compounds of formula II, R^1 is $C(O)R^3$.

In other specific compounds of formula II, R^3 is (C_0-C_4) alkyl- (C_2-C_5) heteroaryl, (C_1-C_8) alkyl, aryl, or (C_0-C_4) alkyl- OR^5 .

In other specific compounds of formula II, heteroaryl is pyridyl, furyl, or thienyl.

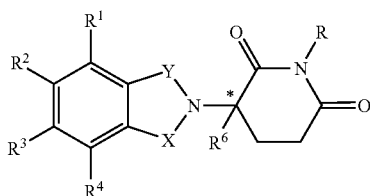
In other specific compounds of formula II, R^1 is $C(O)OR^4$.

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In other specific compounds of formula II, the H of C(O)NHC(O) can be replaced with (C₁-C₄)alkyl, aryl, or benzyl.

Still other specific immunomodulatory compounds of the invention belong to a class of isoindole-imides disclosed in U.S. patent application Ser. No. 09/781,179, International Publication No. WO 98/54170, and U.S. Pat. No. 6,395,754, each of which are incorporated herein by reference. Representative compounds are of formula III:



and pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, and mixtures of stereoisomers thereof, wherein:

one of X and Y is C=O and the other is CH₂ or C=O;
R is H or CH₂OCOR⁵;

(i) each of R¹, R², R³, or R⁴, independently of the others, is halo, alkyl of 1 to 4 carbon atoms, or alkoxy of 1 to 4 carbon atoms or (ii) one of R¹, R², R³, or R⁴ is nitro or —NHR⁵ and the remaining of R¹, R², R³, or R⁴ are hydrogen;

R⁵ is hydrogen or alkyl of 1 to 8 carbons

R⁶ hydrogen, alkyl of 1 to 8 carbon atoms, benzo, chloro, or fluoro;

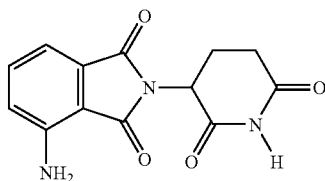
R⁷ is R⁷—CHR¹⁰—N(R⁸R⁹);

R⁷ is m-phenylene or p-phenylene or —(C_nH_{2n})— in which n has a value of 0 to 4;

each of R⁸ and R⁹ taken independently of the other is hydrogen or alkyl of 1 to 8 carbon atoms, or R⁸ and R⁹ taken together are tetramethylene, pentamethylene, hexamethylene, or —CH₂CH₂[X]X₁CH₂CH₂— in which [X]X₁ is —O—, —S—, or —NH—;

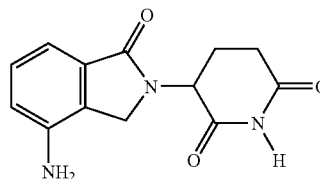
R¹⁰ is hydrogen, alkyl of 1 to 8 carbon atoms, or phenyl; and
* represents a chiral-carbon center.

The most preferred immunomodulatory compounds of the invention are 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione and 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. The compounds can be obtained via standard, synthetic methods (see e.g., U.S. Pat. No. 5,635,517, incorporated herein by reference). The compounds are available from Celgene Corporation, Warren, N.J. 4-(Amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (ACTIMID™) has the following chemical structure:



The compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (REVIMID™) has the following chemical structure:

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Compounds of the invention can either be commercially purchased or prepared according to the methods described in the patents or patent publications disclosed herein. Further, optically pure compounds can be asymmetrically synthesized or resolved using known resolving agents or chiral columns as well as other standard synthetic organic chemistry techniques.

As used herein and unless otherwise indicated, the term “pharmaceutically acceptable salt” encompasses non-toxic acid and base addition salts of the compound to which the term refers. Acceptable non-toxic acid addition salts include those derived from organic and inorganic acids or bases known in the art, which include, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embolic acid, enanthic acid, and the like.

Compounds that are acidic in nature are capable of forming salts with various pharmaceutically acceptable bases. The bases that can be used to prepare pharmaceutically acceptable base addition salts of such acidic compounds are those that form non-toxic base addition salts, i.e., salts containing pharmacologically acceptable cations such as, but not limited to, alkali metal or alkaline earth metal salts and the calcium, magnesium, sodium or potassium salts in particular. Suitable organic bases include, but are not limited to, N,N-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), lysine, and procaine.

As used herein and unless otherwise indicated, the term “prodrug” means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide the compound. Examples of prodrugs include, but are not limited to, derivatives of immunomodulatory compounds of the invention that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of immunomodulatory compounds of the invention that comprise —NO, —NO₂, —ONO, or —ONO₂ moieties. Prodrugs can typically be prepared using well-known methods, such as those described in 1 *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed. 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elsevier, New York 1985).

As used herein and unless otherwise indicated, the terms “biohydrolyzable amide,” “biohydrolyzable ester,” “biohydrolyzable carbamate,” “biohydrolyzable carbonate,” “biohydrolyzable ureide,” “biohydrolyzable phosphate” mean an amide, ester, carbamate, carbonate, ureide, or phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as

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uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, lower acyloxyalkyl esters (such as acetoxymethyl, acetoxylethyl, aminocarbonyloxymethyl, pivaloyloxymethyl, and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxycarbonyloxymethyl, ethoxycarbonyloxyethyl and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters, and acylamino alkyl esters (such as acetamidomethyl esters). Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α -amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted ethylenediamines, amino acids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

Various immunomodulatory compounds of the invention contain one or more chiral centers, and can exist as racemic mixtures of enantiomers or mixtures of diastereomers. This invention encompasses the use of stereomerically pure forms of such compounds, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular immunomodulatory compounds of the invention may be used in methods and compositions of the invention. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. See, e.g., Jacques, J., et al., *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., et al., *Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E. L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, Ind., 1972).

As used herein and unless otherwise indicated, the term "stereomerically pure" means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. As used herein and unless otherwise indicated, the term "stereomerically enriched" means a composition that comprises greater than about 60% by weight of one stereoisomer of a compound, preferably greater than about 70% by weight, more preferably greater than about 80% by weight of one stereoisomer of a compound. As used herein and unless otherwise indicated, the term "enantiomerically pure" means a stereomerically pure composition of a compound having one chiral center.

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Similarly, the term "stereomerically enriched" means a stereomerically enriched composition of a compound having one chiral center.

It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

5.2 Second Active Agents

Immunomodulatory compounds can be combined with other pharmacologically active compounds ("second active agents") in methods and compositions of the invention. It is believed that certain combinations work synergistically in the treatment of particular types of cancer and certain diseases and conditions associated with, or characterized by, undesired angiogenesis. Immunomodulatory compounds can also work to alleviate adverse effects associated with certain second active agents, and some second active agents can be used to alleviate adverse effects associated with immunomodulatory compounds.

One or more second active ingredients or agents can be used in the methods and compositions of the invention together with an immunomodulatory compound. Second active agents can be large molecules (e.g., proteins) or small molecules (e.g., synthetic inorganic, organometallic, or organic molecules).

Examples of large molecule active agents include, but are not limited to, hematopoietic growth factors, cytokines, and monoclonal and polyclonal antibodies. Typical large molecule active agents are biological molecules, such as naturally occurring or artificially made proteins. Proteins that are particularly useful in this invention include proteins that stimulate the survival and/or proliferation of hematopoietic precursor cells and immunologically active poietic cells in vitro or in vivo. Others stimulate the division and differentiation of committed erythroid progenitors in cells in vitro or in vivo. Particular proteins include, but are not limited to: interleukins, such as IL-2 (including recombinant IL-11 ("rIL2") and canarypox IL-2), IL-10, IL-12, and IL-18; interferons, such as interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon beta-1 a, and interferon gamma-1 b; GM-CSF and GM-CSF; and EPO.

Particular proteins that can be used in the methods and compositions of the invention include, but are not limited to: filgrastim, which is sold in the United States under the trade name Neupogen® (Amgen, Thousand Oaks, Calif.); sargramostim, which is sold in the United States under the trade name Leukine® (Immunex, Seattle, Wash.); and recombinant EPO, which is sold in the United States under the trade name Epogen® (Amgen, Thousand Oaks, Calif.).

Recombinant and mutated forms of GM-CSF can be prepared as described in U.S. Pat. Nos. 5,391,485; 5,393,870; and 5,229,496; all of which are incorporated herein by reference. Recombinant and mutated forms of G-CSF can be prepared as described in U.S. Pat. Nos. 4,810,643; 4,999,291; 5,528,823; and 5,580,755; all of which are incorporated herein by reference.

This invention encompasses the use of native, naturally occurring, and recombinant proteins. The invention further encompasses mutants and derivatives (e.g., modified forms) of naturally occurring proteins that exhibit, in vivo, at least some of the pharmacological activity of the proteins upon which they are based. Examples of mutants include, but are

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not limited to, proteins that have one or more amino acid residues that differ from the corresponding residues in the naturally occurring forms of the proteins. Also encompassed by the term "mutants" are proteins that lack carbohydrate moieties normally present in their naturally occurring forms (e.g., nonglycosylated forms). Examples of derivatives include, but are not limited to, pegylated derivatives and fusion proteins, such as proteins formed by fusing IgG1 or IgG3 to the protein or active portion of the protein of interest. See, e.g., Penichet, M. L. and Morrison, S. L., *J. Immunol. Methods* 248:91-101 (2001).

Antibodies that can be used in combination with compounds of the invention include monoclonal and polyclonal antibodies. Examples of antibodies include, but are not limited to, trastuzumab (Herceptin®), rituximab (Rituxan®), bevacizumab (Avastin™), pertuzumab (Omnitarg™), tositumomab (Bexxar®), edrecolomab (Panorex®), and G250. Compounds of the invention can also be combined with, or used in combination with, anti-TNF- α antibodies.

Large molecule active agents may be administered in the form of anti-cancer vaccines. For example, vaccines that secrete, or cause the secretion of, cytokines such as IL-2, G-CSF, and GM-CSF can be used in the methods, pharmaceutical compositions, and kits of the invention. See, e.g., Emens, L. A., et al., *Curr. Opinion Mol. Ther.* 3(1):77-84 (2001).

In one embodiment of the invention, the large molecule active agent reduces, eliminates, or prevents an adverse effect associated with the administration of an immunomodulatory compound. Depending on the particular immunomodulatory compound and the disease or disorder being treated, adverse effects can include, but are not limited to, drowsiness and somnolence, dizziness and orthostatic hypotension, neutropenia, infections that result from neutropenia, increased HIV-viral load, bradycardia, Stevens-Johnson Syndrome and toxic epidermal necrolysis, and seizures (e.g., grand mal convulsions). A specific adverse effect is neutropenia.

Second active agents that are small molecules can also be used to alleviate adverse effects associated with the administration of an immunomodulatory compound. However, like some large molecules, many are believed to be capable of providing a synergistic effect when administered with (e.g., before, after or simultaneously) an immunomodulatory compound. Examples of small molecule second active agents include, but are not limited to, anti-cancer agents, antibiotics, immunosuppressive agents, and steroids.

Examples of anti-cancer agents include, but are not limited to: acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; celecoxib (COX-2 inhibitor); chlorambucil; cirolemycin; cisplatin; cladribine; crisanol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; diazomycin; edatrexate; eflomithine hydrochloride; elsamitucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; eto-

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prine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofofosine; iproplatin; irinotecan; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; pipsulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; safinol; safinol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiro-mustine; spirolatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; taxotere; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazo-furin; tirapazamine; toremifene citrate; tretolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; and zorubicin hydrochloride.

Other anti-cancer drugs include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; antidorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; brefflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; capecitabine; carboxamide-amino-triazole; carboxamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlins; chloroquinoloxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisanol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatan; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydridemnin B; deslorelin; dexamethasone; dexifosfamide; dextrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnor-

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spermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; doxorubicin; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflomithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofofosine; ilomastat; imatinib (e.g., Gleevec®), imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuporelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; loroxibine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocold; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mitoguanzone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; Erbitux, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; oblimersen (Genasense®); O⁶-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors; microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhodium Re 186 etidronate; rhizoxin; ribozymes; R11 retinamide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim;

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Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotripan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; toposentin; toremifene; translation inhibitors; tretinoin; triacetyluridine; triceribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer.

Specific second active agents include, but are not limited to, oblimersen (Genasense®), remicade, docetaxel, celecoxib, melphalan, dexamethasone (Decadron®), steroids, gemcitabine, cisplatin, temozolomide, etoposide, cyclophosphamide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, topotecan, methotrexate, Arisa®, taxol, taxotere, fluorouracil, leucovorin, irinotecan, xeloda, CPT-11, interferon alpha, pegylated interferon alpha (e.g., PEG INTRON-A), capecitabine, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxol, paclitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil®), paclitaxel, ganciclovir, adriamycin, estramustine sodium phosphate (Emcyt®), sulindac, and etoposide.

5.3 Methods of Treatments and Prevention

Methods of this invention encompass methods of treating, preventing and/or managing various types of cancer and diseases and disorders associated with, or characterized by, undesired angiogenesis. As used herein, unless otherwise specified, the term “treating” refers to the administration of a compound of the invention or other additional active agent after the onset of symptoms of the particular disease or disorder. As used herein, unless otherwise specified, the term “preventing” refers to the administration prior to the onset of symptoms, particularly to patients at risk of cancer, and other diseases and disorders associated with, or characterized by, undesired angiogenesis. The term “prevention” includes the inhibition of a symptom of the particular disease or disorder. Patients with familial history of cancer and diseases and disorders associated with, or characterized by, undesired angiogenesis are preferred candidates for preventive regimens. As used herein and unless otherwise indicated, the term “managing” encompasses preventing the recurrence of the particular disease or disorder in a patient who had suffered from it, and/or lengthening the time a patient who had suffered from the disease or disorder remains in remission.

As used herein, the term “cancer” includes, but is not limited to, solid tumors and blood born tumors. The term “cancer” refers to disease of skin tissues, organs, blood, and vessels, including, but not limited to, cancers of the bladder, bone or blood, brain, breast, cervix, chest, colon,

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endometrium, esophagus, eye, head, kidney, liver, lymph nodes, lung, mouth, neck, ovaries, pancreas, prostate, rectum, stomach, testis, throat, and uterus. Specific cancers include, but are not limited to, advanced malignancy, amyloidosis, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, recurrent malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, malignant melanoma, malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scleroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unresectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and leiomyoma. In a specific embodiment, the cancer is metastatic. In another embodiment, the cancer is refractory or resistance to chemotherapy or radiation; in particular, refractory to thalidomide.

As used herein to refer to diseases and conditions other than cancer, the terms "diseases or disorders associated with, or characterized by, undesired angiogenesis," "diseases or disorders associated with undesired angiogenesis," and "diseases or disorders characterized by undesired angiogenesis" refer to diseases, disorders and conditions that are caused, mediated or attended by undesired, unwanted or uncontrolled angiogenesis, including, but not limited to, inflammatory diseases, autoimmune diseases, genetic diseases, allergic diseases, bacterial diseases, ocular neovascular diseases, choroidal neovascular diseases, and retina neovascular diseases.

Examples of such diseases or disorders associated with undesired angiogenesis include, but are not limited to, diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, proliferative vitreoretinopathy, trachoma, myopia, optic pits, epidemic keratoconjunctivitis, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, sjogrens, acne rosacea, phlyctenulosis, syphilis, lipid degeneration, bacterial ulcer, fungal ulcer, Herpes simplex infection, Herpes zoster infection, protozoan infection, Kaposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, marginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis, trauma, Wegeners sarcoidosis, Scleritis, Steven's Johnson disease, peripheral radial keratotomy, sickle cell anemia, sarcoid, pseudoxanthoma elasticum, Pagets disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, Eales disease, Bechets disease, retinitis, choroiditis, presumed ocular histoplasmosis, Bests disease, Stargarts disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, rubeosis, sarcoidosis, sclerosis, soriatis, psoriasis, primary sclerosing cholangitis, proctitis, primary biliary srosis, idiopathic pulmonary fibrosis, and alcoholic hepatitis.

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In specific embodiments of the invention, diseases or disorders associated with undesired angiogenesis do not include congestive heart failure, cardiomyopathy, pulmonary edema, endotoxin-mediated septic shock, acute viral myocarditis, cardiac allograft rejection, myocardial infarction, HIV, hepatitis, adult respiratory distress syndrome, bone-resorption disease, chronic obstructive pulmonary diseases, chronic pulmonary inflammatory disease, dermatitis, cystic fibrosis, septic shock, sepsis, endotoxic shock, hemodynamic shock, sepsis syndrome, post ischemic reperfusion injury, meningitis, psoriasis, fibrotic disease, cachexia, graft rejection, rheumatoid spondylitis, osteoporosis, Crohn's disease, ulcerative colitis, inflammatory-bowel disease, multiple sclerosis, systemic lupus erythematosus, erythema nodosum leprosum in leprosy, radiation damage, asthma, hyperoxic alveolar injury, malaria, mycobacterial infection, and opportunistic infections resulting from HIV.

This invention encompasses methods of treating patients who have been previously treated for cancer or diseases or disorders associated with, or characterized by, undesired angiogenesis, but are non-responsive to standard therapies, as well as those who have not previously been treated. The invention also encompasses methods of treating patients regardless of patient's age, although some diseases or disorders are more common in certain age groups. The invention further encompasses methods of treating patients who have undergone surgery in an attempt to treat the disease or condition at issue, as well as those who have not. Because patients with cancer and diseases and disorders characterized by undesired angiogenesis have heterogeneous clinical manifestations and varying clinical outcomes, the treatment given to a patient may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation specific secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual patient with cancer and other diseases or disorders.

Methods encompassed by this invention comprise administering one or more immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, to a patient (e.g., a human) suffering, or likely to suffer, from cancer or a disease or disorder mediated by undesired angiogenesis.

In one embodiment of the invention, an immunomodulatory compound of the invention can be administered orally and in single or divided daily doses in an amount of from about 0.10 to about 150 mg/day. In a particular embodiment, 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (Actimid™) may be administered in an amount of from about 0.1 to about 1 mg per day, or alternatively from about 0.1 to about 5 mg every other day. In a preferred embodiment, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revimid™) may be administered in an amount of from about 5 to 25 mg per day, or alternatively from about 10 to about 50 mg every other day.

In a specific embodiment, 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (Actimid™) may be administered in an amount of about 1, 2, or 5 mg per day to patients with relapsed multiple myeloma. In a particular embodiment, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revimid™) may be administered initially in an amount of 5 mg/day and the dose can be escalated every week to 10, 20, 25, 30 and 50 mg/day. In a specific embodiment, Revimid™ can be administered in an amount of up to about 30 mg/day to patients with solid tumor. In a particular

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embodiment, Revimid™ can be administered in an amount of up to about 40 mg/day to patients with glioma.

5.3.1 Combination Therapy with a Second Active Agent

Specific methods of the invention comprise administering an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, in combination with one or more second active agents, and/or in combination with radiation therapy, blood transfusions, or surgery. Examples of immunomodulatory compounds of the invention are disclosed herein (see, e.g., section 5.1). Examples of second active agents are also disclosed herein (see, e.g., section 5.2).

Administration of the immunomodulatory compounds and the second active agents to a patient can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. A preferred route of administration for an immunomodulatory compound of the invention is orally. Preferred routes of administration for the second active agents or ingredients of the invention are known to those of ordinary skill in the art. See, e.g., *Physicians' Desk Reference*, 1755-1760 (56th ed., 2002).

In one embodiment of the invention, the second active agent is administered intravenously or subcutaneously and once or twice daily in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of disease, and the amount(s) of immunomodulatory compounds of the invention and any optional additional active agents concurrently administered to the patient. In a particular embodiment, the second active agent is oblimersen (Genasense®), GM-CSF, G-CSF, EPO, taxotere, irinotecan, dacarbazine, transretinoic acid, topotecan, pentoxifylline, ciprofloxacin, dexamethasone, vincristine, doxorubicin, COX-2 inhibitor, IL2, IL8, IL18, IFN, Ara-C, vinorelbine, or a combination thereof.

In a particular embodiment, GM-CSF, G-CSF or EPO is administered subcutaneously during about five days in a four or six week cycle in an amount of from about 1 to about 750 mg/m²/day, preferably in an amount of from about 25 to about 500 mg/m²/day, more preferably in an amount of from about 50 to about 250 mg/m²/day, and most preferably in an amount of from about 50 to about 200 mg/m²/day. In a certain embodiment, GM-CSF may be administered in an amount of from about 60 to about 500 mcg/m² intravenously over 2 hours, or from about 5 to about 12 mcg/m²/day subcutaneously. In a specific embodiment, G-CSF may be administered subcutaneously in an amount of about 1 mcg/kg/day initially and can be adjusted depending on rise of total granulocyte counts. The maintenance dose of G-CSF may be administered in an amount of about 300 (in smaller patients) or 480 mcg subcutaneously. In a certain embodiment, EPO may be administered subcutaneously in an amount of 10,000 Unit 3 times per week.

In another embodiment, Revimid™ in an amount of about 25 mg/d and dacarbazine in an amount of about from 200 to 1,000 mg/m²/d are administered to patients with metastatic malignant melanoma. In a specific embodiment, Revimid™ is administered in an amount of from about 5 to about 25 mg/d

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to patients with metastatic malignant melanoma whose disease has progressed on treatment with dacarbazine, IL-2 or IFN. In a specific embodiment, Revimid™ is administered to patients with relapsed or refractory multiple myeloma in an amount of about 15 mg/d twice a day or about 30 mg/d four times a day in a combination with dexamethasone.

In another embodiment, an immunomodulatory compound is administered with melphalan and dexamethasone to patients with amyloidosis. In a specific embodiment, an immunomodulatory compound of the invention and steroids can be administered to patients with amyloidosis.

In another embodiment, an immunomodulatory compound is administered with gemcitabine and cisplatin to patients with locally advanced or metastatic transitional cell bladder cancer.

In another embodiment, an immunomodulatory compound is administered in combination with a second active ingredient as follows: temozolomide to pediatric patients with relapsed or progressive brain tumors or recurrent neuroblastoma; celecoxib, etoposide and cyclophosphamide for relapsed or progressive CNS cancer; temodar to patients with recurrent or progressive meningioma, malignant meningioma, hemangiopericytoma, multiple brain metastases, relapsed brain tumors, or newly diagnosed glioblastoma multiformis; irinotecan to patients with recurrent glioblastoma; carboplatin to pediatric patients with brain stem glioma; procarbazine to pediatric patients with progressive malignant gliomas; cyclophosphamide to patients with poor prognosis malignant brain tumors, newly diagnosed or recurrent glioblastoma multiformis; Gliadel® for high grade recurrent malignant gliomas; temozolomide and tamoxifen for anaplastic astrocytoma; or topotecan for gliomas, glioblastoma, anaplastic astrocytoma or anaplastic oligodendroglioma.

In another embodiment, an immunomodulatory compound is administered with methotrexate and cyclophosphamide to patients with metastatic breast cancer.

In another embodiment, an immunomodulatory compound is administered with temozolomide to patients with neuroendocrine tumors.

In another embodiment, an immunomodulatory compound is administered with gemcitabine to patients with recurrent or metastatic head or neck cancer. In another embodiment, an immunomodulatory compound is administered with gemcitabine to patients with pancreatic cancer.

In another embodiment, an immunomodulatory compound is administered to patients with colon cancer in combination with Arisa®, taxol and/or taxotere.

In another embodiment, an immunomodulatory compound is administered with capecitabine to patients with refractory colorectal cancer or patients who fail first line therapy or have poor performance in colon or rectal adenocarcinoma.

In another embodiment, an immunomodulatory compound is administered in combination with fluorouracil, leucovorin, and irinotecan to patients with Dukes C & D colorectal cancer or to patients who have been previously treated for metastatic colorectal cancer.

In another embodiment, an immunomodulatory compound is administered to patients with refractory colorectal cancer in combination with capecitabine, xeloda, and/or CPT-11.

In another embodiment, an immunomodulatory compound of the invention is administered with capecitabine and irinotecan to patients with refractory colorectal cancer or to patients with unresectable or metastatic colorectal carcinoma.

In another embodiment, an immunomodulatory compound is administered alone or in combination with interferon alpha or capecitabine to patients with unresectable or metastatic

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hepatocellular carcinoma; or with cisplatin and thiotepa to patients with primary or metastatic liver cancer.

In another embodiment, an immunomodulatory compound is administered in combination with pegylated interferon alpha to patients with Kaposi's sarcoma.

In another embodiment, an immunomodulatory compound is administered in combination with fludarabine, carboplatin, and/or topotecan to patients with refractory or relapsed or high-risk acuted myelogenous leukemia.

In another embodiment, an immunomodulatory compound is administered in combination with liposomal daunorubicin, topotecan and/or cytarabine to patients with unfavorable karyotype acute myeloblastic leukemia.

In another embodiment, an immunomodulatory compound is administered in combination with gemcitabine and irinotecan to patients with non-small cell lung cancer. In one embodiment, an immunomodulatory compound is administered in combination with carboplatin and irinotecan to patients with non-small cell lung cancer. In one embodiment, an immunomodulatory compound is administered with doxetaxol to patients with non-small cell lung cancer who have been previously treated with carbo/VP 16 and radiotherapy.

In another embodiment, an immunomodulatory compound is administered in combination with carboplatin and/or taxotere, or in combination with carboplatin, paclitaxel and/or thoracic radiotherapy to patients with non-small cell lung cancer. In a specific embodiment, an immunomodulatory compound is administered in combination with taxotere to patients with stage IIIB or IV non-small cell lung cancer.

In another embodiment, an immunomodulatory compound of the invention is administered in combination with oblimersen (Genasense®) to patients with small cell lung cancer.

In another embodiment, an immunomodulatory compound is administered alone or in combination with a second active ingredient such as vinblastine or fludarabine to patients with various types of lymphoma, including, but not limited to, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma or relapsed or refractory low grade follicular lymphoma.

In another embodiment, an immunomodulatory compound is administered in combination with taxotere, IL-2, IFN, GM-CSF, and/or dacarbazine to patients with various types or stages of melanoma.

In another embodiment, an immunomodulatory compound is administered alone or in combination with vinorelbine to patients with malignant mesothelioma, or stage IIIB non-small cell lung cancer with pleural implants or malignant pleural effusion mesothelioma syndrome.

In another embodiment, an immunomodulatory compound is administered to patients with various types or stages of multiple myeloma in combination with dexamethasone, zoledronic acid, palmitronate, GM-CSF, biacin, vinblastine, melphalan, busulphan, cyclophosphamide, IFN, palmidronate, prednisone, bisphosphonate, celecoxib, arsenic trioxide, PEG INTRON-A, vincristine, or a combination thereof.

In another embodiment, an immunomodulatory compound is administered to patients with relapsed or refractory multiple myeloma in combination with doxorubicin (Doxil®), vincristine and/or dexamethasone (Decadron®).

In another embodiment, an immunomodulatory compound is administered to patients with various types or stages of ovarian cancer such as peritoneal carcinoma, papillary serous carcinoma, refractory ovarian cancer or recurrent ovarian

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cancer, in combination with taxol, carboplatin, doxorubicin, gemcitabine, cisplatin, xeloda, paclitaxel, dexamethasone, or a combination thereof.

In another embodiment, an immunomodulatory compound is administered to patients with various types or stages of prostate cancer, in combination with xeloda, 5 FU/LV, gemcitabine, irinotecan plus gemcitabine, cyclophosphamide, vincristine, dexamethasone, GM-CSF, celecoxib, taxotere, ganciclovir, paclitaxel, adriamycin, docetaxel, estramustine, Emcyf, or a combination thereof.

In another embodiment, an immunomodulatory compound is administered to patients with various types or stages of renal cell cancer, in combination with capecitabine, IFN, tamoxifen, IL-2, GM-CSF, Celebrex®, or a combination thereof.

In another embodiment, an immunomodulatory compound is administered to patients with various types or stages of gynecologic, uterus or soft tissue sarcoma cancer in combination with IFN, a COX-2 inhibitor such as Celebrex®, and/or sulindac.

In another embodiment, an immunomodulatory compound is administered to patients with various types or stages of solid tumors in combination with celebrex, etoposide, cyclophosphamide, docetaxel, apecitabine, IFN, tamoxifen, IL-2, GM-CSF, or a combination thereof.

In another embodiment, an immunomodulatory compound is administered to patients with scleroderma or cutaneous vasculitis in combination with celebrex, etoposide, cyclophosphamide, docetaxel, apecitabine, IFN, tamoxifen, IL-2, GM-CSF, or a combination thereof.

This invention also encompasses a method of increasing the dosage of an anti-cancer drug or agent that can be safely and effectively administered to a patient, which comprises administering to a patient (e.g., a human) an immunomodulatory compound of the invention, or a pharmaceutically acceptable derivative, salt, solvate, clathrate, hydrate, or pro-drug thereof. Patients that can benefit by this method are those likely to suffer from an adverse effect associated with anti-cancer drugs for treating a specific cancer of the skin, subcutaneous tissue, lymph nodes, brain, lung, liver, bone, intestine, colon, heart, pancreas, adrenal, kidney, prostate, breast, colorectal, or combinations thereof. The administration of an immunomodulatory compound of the invention alleviates or reduces adverse effects which are of such severity that it would otherwise limit the amount of anti-cancer drug.

In one embodiment, an immunomodulatory compound of the invention can be administered orally and daily in an amount of from about 0.1 to about 150 mg, and preferably from about 1 to about 50 mg, more preferably from about 2 to about 25 mg prior to, during, or after the occurrence of the adverse effect associated with the administration of an anti-cancer drug to a patient. In a particular embodiment, an immunomodulatory compound of the invention is administered in combination with specific agents such as heparin, aspirin, coumadin, or G-CSF to avoid adverse effects that are associated with anti-cancer drugs such as but not limited to neutropenia or thrombocytopenia.

In one embodiment, an immunomodulatory compound of the invention can be administered to patients with diseases and disorders associated with, or characterized by, undesired angiogenesis in combination with additional active ingredients including but not limited to anti-cancer drugs, anti-inflammatories, antihistamines, antibiotics, and steroids.

In another embodiment, this invention encompasses a method of treating, preventing and/or managing cancer, which comprises administering an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt,

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solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, in conjunction with (e.g. before, during, or after) conventional therapy including, but not limited to, surgery, immunotherapy, biological therapy, radiation therapy, or other non-drug based therapy presently used to treat, prevent or manage cancer. The combined use of the immunomodulatory compounds of the invention and conventional therapy may provide a unique treatment regimen that is unexpectedly effective in certain patients. Without being limited by theory, it is believed that immunomodulatory compounds of the invention may provide additive or synergistic effects when given concurrently with conventional therapy.

As discussed elsewhere herein, the invention encompasses a method of reducing, treating and/or preventing adverse or undesired effects associated with conventional therapy including, but not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy. One or more immunomodulatory compounds of the invention and other active ingredient can be administered to a patient prior to, during, or after the occurrence of the adverse effect associated with conventional therapy.

In one embodiment, an immunomodulatory compound of the invention can be administered in an amount of from about 0.1 to about 150 mg, and preferably from about 1 to about 25 mg, more preferably from about 2 to about 10 mg orally and daily alone, or in combination with a second active agent disclosed herein (see, e.g., section 5.2), prior to, during, or after the use of conventional therapy.

In a specific embodiment of this method, an immunomodulatory compound of the invention and doxorubicin are administered to patients with non-small cell lung cancer who were previously treated with carboplatin and radiotherapy.

5.3.2 Use with Transplantation Therapy

Compounds of the invention can be used to reduce the risk of Graft Versus Host Disease (GVHD). Therefore, the invention encompasses a method of treating, preventing and/or managing cancer, which comprises administering the immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, in conjunction with transplantation therapy.

As those of ordinary skill in the art are aware, the treatment of cancer is often based on the stages and mechanism of the disease. For example, as inevitable leukemic transformation develops in certain stages of cancer, transplantation of peripheral blood stem cells, hematopoietic stem cell preparation or bone marrow may be necessary. The combined use of the immunomodulatory compound of the invention and transplantation therapy provides a unique and unexpected synergism. In particular, an immunomodulatory compound of the invention exhibits immunomodulatory activity that may provide additive or synergistic effects when given concurrently with transplantation therapy in patients with cancer.

An immunomodulatory compound of the invention can work in combination with transplantation therapy reducing complications associated with the invasive procedure of transplantation and risk of GVHD. This invention encompasses a method of treating, preventing and/or managing cancer which comprises administering to a patient (e.g., a human) an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof, before, during, or after the transplantation of umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow. Examples of stem cells suitable for use

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in the methods of the invention are disclosed in U.S. provisional patent application No. 60/372,348, filed Apr. 12, 2002 by R. Hariri et al., the entirety of which is incorporated herein by reference.

In one embodiment of this method, an immunomodulatory compound of the invention is administered to patients with multiple myeloma before, during, or after the transplantation of autologous peripheral blood progenitor cell.

In another embodiment, an immunomodulatory compound is administered to patients with relapsing multiple myeloma after the stem cell transplantation.

In another embodiment, an immunomodulatory compound and prednisone are administered as maintenance therapy to patients with multiple myeloma following the transplantation of autologous stem cell.

In another embodiment, an immunomodulatory compound and dexamethasone are administered as salvage therapy for low risk post transplantation to patients with multiple myeloma.

In another embodiment, an immunomodulatory compound and dexamethasone are administered as maintenance therapy to patients with multiple myeloma following the transplantation of autologous bone marrow.

In another embodiment, an immunomodulatory compound is administered following the administration of high dose of melphalan and the transplantation of autologous stem cell to patients with chemotherapy responsive multiple myeloma.

In another embodiment, an immunomodulatory compound and PEG INTRO-A are administered as maintenance therapy to patients with multiple myeloma following the transplantation of autologous CD34-selected peripheral stem cell.

In another embodiment, an immunomodulatory compound is administered with post transplant consolidation chemotherapy to patients with newly diagnosed multiple myeloma to evaluate anti-angiogenesis.

In another embodiment, an immunomodulatory compound and dexamethasone are administered as maintenance therapy after DCEP consolidation, following the treatment with high dose of melphalan and the transplantation of peripheral blood stem cell to 65 years of age or older patients with multiple myeloma.

5.3.3 Cycling Therapy

In certain embodiments, the prophylactic or therapeutic agents of the invention are cyclically administered to a patient. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

Consequently, in one specific embodiment of the invention, an immunomodulatory compound of the invention is administered daily in a single or divided doses in a four to six week cycle with a rest period of about a week or two weeks. The invention further allows the frequency, number, and length of dosing cycles to be increased. Thus, another specific embodiment of the invention encompasses the administration of an immunomodulatory compound of the invention for more cycles than are typical when it is administered alone. In yet another specific embodiment of the invention, an immunomodulatory compound of the invention is administered for a greater number of cycles that would typically cause dose-limiting toxicity in a patient to whom a second active ingredient is not also being administered.

In one embodiment, an immunomodulatory compound of the invention is administered daily and continuously for three or four weeks at a dose of from about 0.1 to about 150 mg/d followed by a break of one or two weeks. Actimid™ is preferably administered daily and continuously at an initial dose of 0.1 to 5 mg/d with dose escalation (every week) by 1 to 10 mg/d to a maximum dose of 50 mg/d for as long as therapy is tolerated. In a particular embodiment, Revimid™ is administered in an amount of about 5, 10, or 25 mg/day, preferably in an amount of about 10 mg/day for three to four weeks, followed by one week or two weeks of rest in a four or six week cycle.

In one embodiment of the invention, an immunomodulatory compound of the invention and a second active ingredient are administered orally, with administration of an immunomodulatory compound of the invention occurring 30 to 60 minutes prior to a second active ingredient, during a cycle of four to six weeks. In another embodiment of the invention, the combination of an immunomodulatory compound of the invention and a second active ingredient is administered by intravenous infusion over about 90 minutes every cycle. In a specific embodiment, one cycle comprises the administration of from about 10 to about 25 mg/day of Revimid™ and from about 50 to about 200 mg/m²/day of a second active ingredient daily for three to four weeks and then one or two weeks of rest. In another specific embodiment, each cycle comprises the administration of from about 5 to about 10 mg/day of Actimid™ and from about 50 to about 200 mg/m²/day of a second active ingredient for 3 to 4 weeks followed by one or two weeks of rest. Typically, the number of cycles during which the combinatorial treatment is administered to a patient will be from about one to about 24 cycles, more typically from about two to about 16 cycles, and even more typically from about four to about three cycles.

5.4 Pharmaceutical Compositions and Dosage Forms

Pharmaceutical compositions can be used in the preparation of individual, single unit dosage forms. Pharmaceutical compositions and dosage forms of the invention comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof. Pharmaceutical compositions and dosage forms of the invention can further comprise one or more excipients.

Pharmaceutical compositions and dosage forms of the invention can also comprise one or more additional active ingredients. Consequently, pharmaceutical compositions and dosage forms of the invention comprise the active ingredients disclosed herein (e.g., an immunomodulatory compound and a second active agent). Examples of optional second, or additional, active ingredients are disclosed herein (see, e.g., section 5.2).

Single unit dosage forms of the invention are suitable for oral, mucosal (e.g., nasal, sublingual, vaginal, buccal, or rectal), parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical (e.g., eye drops or other ophthalmic preparations), transdermal or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral admin-

istration to a patient; eye drops or other ophthalmic preparations suitable for topical administration; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, e.g., *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton Pa. (1990).

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, this invention encompasses pharmaceutical compositions and dosage forms that contain little, if any, lactose other mono- or disaccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the *U.S. Pharmacopeia* (USP) 25-NF20 (2002). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, N.Y., 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or

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low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs, and strip packs.

The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise an immunomodulatory compound of the invention or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of from about 0.10 to about 150 mg. Typical dosage forms comprise an immunomodulatory compound of the invention or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of about 0.1, 1, 2, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25, 50, 100, 150 or 200 mg. In a particular embodiment, a preferred dosage form comprises 4-(amino-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (Actimid™) in an amount of about 1, 2, 5, 10, 25 or 50 mg. In a specific embodiment, a preferred dosage form comprises 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revimid™) in an amount of about 5, 10, 25 or 50 mg. Typical dosage forms comprise the second active ingredient in an amount of 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. Of course, the specific amount of the anti-cancer drug will depend on the specific agent used, the type of cancer being treated or managed, and the amount(s) of an immunomodulatory compound of the invention and any optional additional active agents concurrently administered to the patient.

5.4.1 Oral Dosage Forms

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton Pa. (1990).

Typical oral dosage forms of the invention are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in

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oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa.), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to

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about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, odium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, ther starches, clays, other algin, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

A preferred solid oral dosage form of the invention comprises an immunomodulatory compound of the invention, anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

5.4.2 Delayed Release Dosage Forms

Active ingredients of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time

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of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

5.4.3 Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention. For example, cyclodextrin and its derivatives can be used to increase the solubility of an immunomodulatory compound of the invention and its derivatives. See, e.g., U.S. Pat. No. 5,134,127, which is incorporated herein by reference.

5.4.4 Topical and Mucosal Dosage Forms

Topical and mucosal dosage forms of the invention include, but are not limited to, sprays, aerosols, solutions, emulsions, suspensions, eye drops or other ophthalmic preparations, or other forms known to one of skill in the art. See, e.g., *Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton Pa. (1980 & 1990); and *Introduction to Pharmaceutical Dosage Forms*, 4th ed., Lea & Febiger, Philadelphia (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes or as oral gels.

Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide topical and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind,

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typical excipients include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof to form solutions, emulsions or gels, which are non-toxic and pharmaceutically acceptable. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. See, e.g., *Remington's Pharmaceutical Sciences*, 16th and 18th eds., Mack Publishing, Easton Pa. (1980 & 1990).

The pH of a pharmaceutical composition or dosage form may also be adjusted to improve delivery of one or more active ingredients. Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of one or more active ingredients so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. Different salts, hydrates or solvates of the active ingredients can be used to further adjust the properties of the resulting composition.

5.4.5 Kits

Typically, active ingredients of the invention are preferably not administered to a patient at the same time or by the same route of administration. This invention therefore encompasses kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a patient.

A typical kit of the invention comprises a dosage form of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt salt, solvate, hydrate, stereoisomer, prodrug, or clathrate thereof. Kits encompassed by this invention can further comprise additional active ingredients such as oblimersen (Genasense®), melphalan, G-CSF, GM-CSF, EPO, topotecan, dacarbazine, irinotecan, taxotere, IFN, COX-2 inhibitor, pentoxifylline, ciprofloxacin, dexamethasone, IL2, IL8, IL18, Ara-C, vinorelbine, isotretinoin, 13 cis-retinoic acid, or a pharmacologically active mutant or derivative thereof, or a combination thereof. Examples of the additional active ingredients include, but are not limited to, those disclosed herein (see, e.g., section 5.2).

Kits of the invention can further comprise devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, drip bags, patches, and inhalers.

Kits of the invention can further comprise cells or blood for transplantation as well as pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

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6. EXAMPLES

Certain embodiments of the invention are illustrated by the following non-limiting examples.

6.1 Modulation of Cytokine Production

A series of non-clinical pharmacology and toxicology studies have been performed to support the clinical evaluation of an immunomodulatory compound of the invention in human subjects. These studies were performed in accordance with internationally recognized guidelines for study design and in compliance with the requirements of Good Laboratory Practice (GLP), unless otherwise noted.

Inhibition of TNF- α production following LPS-stimulation of human PBMC and human whole blood by 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (Ac-timidTM), 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione and thalidomide (RevimidTM) was investigated in vitro (Muller et al., *Bioorg. Med. Chem. Lett.* 9:1625-1630, 1999). The IC₅₀'s of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione for inhibiting production of TNF- α following LPS-stimulation of PBMC and human whole blood were ~24 nM (6.55 ng/mL) and ~25 nM (6.83 ng/mL), respectively. In vitro studies suggest a pharmacological activity profile for 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione that is similar to, but at least 200 times more potent than, thalidomide. In vitro studies have also demonstrated that concentrations of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione of 2.73 to 27.3 ng/mL (0.01 to 0.1 μ M) achieved 50% inhibition of the proliferation of MM.1S and Hs Sultan cells.

The IC₅₀'s of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for inhibiting production of TNF- α following LPS-stimulation of PBMC and human whole blood were ~100 nM (25.9 ng/mL) and ~480 nM (103.6 ng/mL), respectively. Thalidomide, in contrast, had an IC₅₀ of ~194 μ M (50.2 μ g/mL) for inhibiting production of TNF- α following LPS-stimulation of PBMC. In vitro studies suggest a pharmacological activity profile for 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione that is similar to, but 50 to 2000 times more potent than, thalidomide. It has been shown that the compound is approximately 50-100 times more potent than thalidomide in stimulating the proliferation of T-cells following primary induction by T-cell receptor (TCR) activation. 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is also approximately 50 to 100 times more potent than thalidomide in augmenting the production of IL-2 and IFN- γ following TCR activation of PBMC (IL-2) or T-cells (IFN- γ). In addition, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione exhibited dose-dependent inhibition of LPS-stimulated production of the pro-inflammatory cytokines TNF- α , IL-1 β , and IL-6 by PBMC while it increased production of the anti-inflammatory cytokine IL-10.

6.2 Inhibition of MM Cell Proliferation

The ability of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (RevimidTM) and thalidomide for comparison to effect the proliferation of MM cell lines has been investigated in an in vitro study. Uptake [³H]-thymidine by different MM cell lines (MM.1S, Hs Sultan, U266 and RPMI-8226) was measured as an indicator of cell proliferation. Cells were incubated in the presence of compounds for 48 hours; [³H]-thymidine was included for the last 8 hours of the incubation period. Addition of 3-(4-amino-1-oxo-1,3-di-

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hydro-isoindol-2-yl)-piperidine-2,6-dione to MM.1S and Hs Sultan cells resulted in 50% inhibition of cell proliferation at concentrations of 0.4 μ m and 1 μ m, respectively. In contrast, addition of thalidomide at concentrations up to 100 μ m resulted in only 15% and 20% inhibition of cell proliferation in MM.1S and Hs Sultan cells, respectively. These data are summarized in FIG. 1.

6.3 Toxicology Studies

The effects of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revimid™) on cardiovascular and respiratory function are investigated in anesthetized dogs. Two groups of Beagle dogs (2/sex/group) are used. One group receives three doses of vehicle only and the other receives three ascending doses of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (2, 10, and 20 mg/kg). In all cases, doses of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione or vehicle are successively administered via infusion through the jugular vein separated by intervals of at least 30 minutes.

The cardiovascular and respiratory changes induced by 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione are minimal at all doses when compared to the vehicle control group. The only statistically significant difference between the vehicle and treatment groups is a small increase in arterial blood pressure (from 94 mmHg to 101 mmHg) following administration of the low dose of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. This effect lasts approximately 15 minutes and is not seen at higher doses. Deviations in femoral blood flow, respiratory parameters, and Qtc interval are common to both the control and treated groups and are not considered treatment-related.

6.4 Cycling Therapy in Patients

In a specific embodiment, an immunomodulatory compound of the invention are cyclically administered to patients with cancer. Cycling therapy involves the administration of a first agent for a period of time, followed by a rest for a period of time and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

In a specific embodiment, prophylactic or therapeutic agents are administered in a cycle of about 4 to 6 weeks, about once or twice every day. One cycle can comprise the administration of a therapeutic or prophylactic agent for three to four weeks and at least a week or two weeks of rest. The number of cycles administered is from about one to about 24 cycles, more typically from about two to about 16 cycles, and more typically from about four to about eight cycles.

For example, in a cycle of four weeks, on day 1, the administration of 25 mg/d of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is started. On day 22, the administration of the compound is stopped for a week of rest. On day 29, the administration of 25 mg/d 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is begun.

6.5 Clinical Studies in Patients

6.5.1 Treatment of Relapsed Multiple Myeloma

4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (Actimid™) was administered to patients with relapsed/refractory multiple myeloma. The study was conducted in

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compliance with Good Clinical Practices. Patients were at least 18 years old, had been diagnosed with multiple myeloma (with paraprotein in serum and/or urine), and were considered refractory to treatment after at least two cycles of treatment, or have relapsed after two cycles of treatment.

Patients who have progressive disease, according to the Southwest Oncology Group (SWOG) criteria, on their prior regimen are considered treatment refractory. Relapse following remission is defined as >25% increase in M component from baseline levels; reappearance of the M paraprotein that had previously disappeared; or a definite increase in the size and number of lytic bone lesions recognized on radiographs. Patients may have had prior therapy with thalidomide, provided they were able to tolerate the treatment. A Zubrod performance status of 0 to 2 is required for all patients.

4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione is administered to patients at doses of 1, 2, 5, or 10 mg/day for up to four weeks; at each dose level, three patients are initially enrolled. Dosing occurs at approximately the same time each morning; all doses are administered in the fasted state (no eating for at least two hours prior to dosing and two hours after dosing). 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione doses are administered in an ascending fashion such that patients in the first cohort receive the lowest dose of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione (1 mg/day) and escalation to the next higher dose level occurs only following the establishment of safety and tolerability at the current dose. If one out of three patients at any dose level experience dose limiting toxicity (DLT), three additional patients are enrolled at that dose. If none of the three additional patients experience DLT, escalation to the next dose level occurs; dose escalations continue in a similar fashion until the MTD is established or the maximum daily dose (10 mg/day) is attained. However, if one of the three additional patients enrolled experiences DLT, the MTD has been reached. If two or more of the three additional patients enrolled experience DLT, the MTD is judged to have been exceeded and three additional patients are enrolled at the preceding dose level to confirm the MTD. Once the MTD has been identified, four additional patients are enrolled at that dose level so that a total of 10 patients is treated at the MTD.

Blood sampling for analysis of pharmacokinetic parameters is performed on Days 1 and 28 according to the following sampling schedule: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose. An additional blood sample is collected at each weekly visit for the determination of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione levels. Total urine collections are also made with urine pooled according to the following time intervals post-dose: 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours. Safety assessments are made by monitoring adverse events, vital signs, ECGs, clinical laboratory evaluations (blood chemistry, hematology, lymphocyte phenotyping, and urinalysis), and physical examination at specific times during the study.

Results of interim pharmacokinetic analyses obtained following single- and multiple-dose administration of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione to multiple myeloma patients are presented below in Tables 1 and 2. These data show that 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione was steadily absorbed at all dose levels in relapsed multiple myeloma patients. Maximum plasma concentrations occurred at a median T_{max} of between 2.5 and 2.8 hours post-dose at Day 1 and between 3 and 4 hours post-dose at Week 4. At all doses, plasma concentrations declined in a monophasic manner after reaching C_{max} . The start of the elimination phase occurred between 3 and 10 hours post-dose at Day 1 and Week 4, respectively.

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These data also showed that after 4 weeks of dosing, 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione accumulated to a small extent (mean accumulation ratios ~1.02 to 1.52 and ~0.94 to 1.62 for C_{max} and $AUC_{(0-\tau)}$, respectively). There was almost a dose proportional increase in $AUC_{(0-\tau)}$ and C_{max} values with increasing dose. A five-fold higher dose of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione produced a 3.2- and 2.2-fold increase in C_{max} , at Day 1 and Week 4, respectively. Similarly, a 5-fold increase in dose resulted in a 3.6- and 2.3-fold increase in $AUC_{(0-\tau)}$, at Day 1 and Week 4, respectively.

TABLE 1

Pharmacokinetic parameters of Actimid™ in relapsed multiple myeloma patients				
Parameter		1 mg (N = 6)	2 mg (N = 2)	5 mg (N = 3)
Day 1				
C_{max}	ng/mL	15.03 (4.04)	24.4* (12.1)	48.56 (14.03)
t_{max}	h	3.3 (2.6)	2.7* (0.3)	2.3 (0.3)
$AUC_{(0-\infty)}$	ng · h/mL	152.90 (36.62)	279.18 (51.10)	593.10 (335.23)
$AUC_{(0-\tau)}$		134.21 (27.14)	249.57 (29.26)	520.94 (267.32)
$t_{1/2}$	h	7.3 (3.4)	6.3 (1.4)	6.5 (2.2)
CL/F	mL/min	114.75 (29.20)	121.43 (22.22)	182.31 (117.06)
Vz/f	L	69.55 (44.97)	65.31 (2.80)	87.24 (22.61)

τ = 24 hours
N/A = not available

TABLE 2

Pharmacokinetic parameters of Actimid™ following multiple oral doses(1, 2, and 5 mg/day) in relapsed multiple myeloma patients				
Parameter		1 mg (N = 5)	2 mg (N = 2)	5 mg (N = 3)
Week 4				
C_{max}	ng/mL	23.20 (7.48)	30.05* (15.64)	58.07 (38.08)
t_{max}	h	3.6 (1.5)	2.8* (0.3)	5.0 (2.6)
$AUC_{(0-\infty)}$	ng · h/mL	N/A	N/A	N/A
$AUC_{(0-\tau)}$		239.31 (122.59)	269.36 (186.34)	597.24 (354.23)
$t_{1/2}$	h	6.2* (0.6)	7.7 (2.8)	7.8 (4.0)
CL/F	mL/min	87.85 (48.48)	162.68 (112.54)	207.50 (175.41)
Vz/f	L	41.35* (8.84)	95.04 (35.39)	103.95 (27.25)

τ = 24 hours
N/A = not available
*N = 3 patients

6.5.2 Treatment of Relapsed Multiple Myeloma

Two Phase 1 clinical studies of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revimid™) have been conducted to identify the maximum tolerated dose (MTD) in patients with refractory or relapsed multiple myeloma. These studies have also characterized the safety profile of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione when ascending doses of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione were given orally for up to 4 weeks. Patients started 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione treatment at 5 mg/day with subsequent escalation to 10, 25, and 50 mg/day. Patients were enrolled for 28 days at their assigned dose, with the option of extended treatment for those who did not exhibit disease progression or experience dose limiting toxicity (DLT). Patients were evaluated for adverse events at each visit and the severity of these events was graded accord-

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ing to the National Cancer Institute (NCI) Common Toxicity Criteria. Patients were discontinued if they experienced DLT (Grade 3 or greater non-hematological, or Grade 4 hematological toxicity). In this study, 27 patients were enrolled. All patients had relapsed multiple myeloma and 18 (72%) were refractory to salvage therapy. Among these patients, 15 had undergone prior autologous stem cell transplantation and 16 patients had received prior thalidomide treatment. The median number of prior regimens was 3 (range 2 to 6).

Blood and urine samples were collected for analysis of pharmacokinetic parameters on Days 1 and 28. Blood samples were collected according to the following sampling schedule: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours post-dose. In addition, a blood sample was collected at each weekly clinic visit for 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione determination. Total urine was collected and pooled according to the following time intervals post-dose: 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours. Response to treatment was assessed by M-protein quantification (by immunoelectrophoresis) from serum and a 24-hour urine collection, with creatinine clearance and 24-hour protein calculations undertaken at screening, baseline, Weeks 2 and 4, and monthly thereafter (or upon early termination). Bone marrow aspirations and/or tissue biopsy are also performed at Months 3, 6 and 12 if a patient's paraprotein serum concentration or 24-hour urine protein excretion declined to the next lower level, based on best

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response criteria. Preliminary results for the 28-day treatment period are summarized below.

Preliminary pharmacokinetic analyses based on these two studies indicated that AUC and C_{max} values increase proportionally with dose following single and multiple doses in multiple myeloma patients (as was seen in healthy volunteers). Further, there was no evidence of accumulation with multiple dosing as single dose $AUC_{(0-\infty)}$ was comparable to multiple dose $AUC_{0-\tau}$ following the same dose of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. Similar to healthy volunteer studies, double peaks were observed. Exposure in multiple myeloma patients appeared to be slightly higher based on C_{max} and AUC values as compared to healthy male volunteers while clearance in multiple myeloma patients was lower than it was in healthy volunteers, consistent with their poorer renal function (both as a consequence of their age and their disease). Finally, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione half-life in patients was shorter than in healthy volunteers (mean 8 hours, ranging up to 17 hours).

In this study, the first cohort of 3 patients was treated for 28 days at 5 mg/day without any dose limiting toxicity (DLT). The second cohort of 3 patients subsequently commenced therapy at 10 mg/day. Patients in the second 10 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione cohort tolerated treatment well.

6.5.3 Treatment of Solid Tumors

Study with 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revimid™) was conducted in patients with varying types of solid tumors, including malignant melanoma (13), carcinoma of the pancreas (2), carcinoid-unknown primary (1), renal carcinoma (1), breast carcinoma (1) and NSCLC (2). Patients received 5 mg/day 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione for seven days and are subsequently escalated every seven days to 10 mg/day, 25 mg/day, and 50 mg/day for a total of 4 weeks of treatment. Patients who experienced clinical benefit were permitted to continue on treatment as Named Patients.

The study initially enrolled 20 patients and was subsequently amended to enroll 16 additional patients (adrenal carcinoma, NSCLC, malignant mesothelioma, breast cancer, malignant melanoma (8), renal cell cancer (4)) at a higher dose. The 16 additional patients were given weekly escalating doses of 25 mg/day, 50 mg/day, 75 mg/day, 100 mg/day, 125 mg/day, and 150 mg/day over a 6-week period with continuing treatment for an additional six weeks.

The study of Phase 1 study was designed to determine a maximum tolerated dose (MTD) of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in patients with refractory solid tumors and/or lymphoma, as well as to characterize the pharmacokinetic and side effect profiles of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in this patient population. The study design dictates that at least 3 patients must be enrolled at a dose level and have completed 28 days of treatment prior to enrollment of patients at the next higher dose level. Patients in the first cohort began dosing at 5 mg/day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. Patients will be escalated to 10, 20, 25, and 30 mg/day provided there is no toxicity.

In this study, the MTD is defined as the highest dose level in which fewer than two of six patients treated did not experience Grade 3 or greater non-hematological toxicity or Grade 4 or greater hematological toxicity. If, at any given dose level in either study, one out of three patients experiences toxicity, three additional patients must be treated at that

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particular dose. If, however, two out of six patients experience DLT, the MTD is judged to have been exceeded. No further dose escalations are to occur and additional patients are to be enrolled at the previous dose level. The dose of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is escalated until the MTD is achieved or the maximum daily dose of is reached.

No DLTs were reported in the initial group of 20 patients enrolled in the study. Thirteen of the original 20 trial patients, along with 2 non-trial patients, continued on treatment as named patients at doses up to 150 mg/day.

6.5.4 Treatment of Gliomas

This study was performed to find toxicity in patients with recurrent, high-grade gliomas. The study is designed such that patients are given increasingly higher doses of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione until a maximum tolerated dose (MTD) is established. The study also seeks to obtain preliminary toxicity information and pharmacokinetic data on 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, as well as to develop exploratory data concerning surrogate end points of angiogenic activity in vivo using functional neuro-imaging studies, and in vitro assays of serum angiogenic peptides.

Patients enrolled in the first cohort receive 2.5 mg/m²/day for a 4-week cycle. During each 4-week cycle of therapy, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered once daily for 3 weeks followed by a week of rest. Patients who complete a treatment cycle may receive another cycle of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione treatment if two criteria are met. First, the patient must have stable disease or have experienced a partial response or complete response, or the patient is benefiting from the therapy with 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione as evidenced by a decrease in tumor-related symptoms such as neurological deficits. Second, the patient must have recovered from toxicity related to 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione which occurred in the prior cycle by Day 42 or sooner (28-day cycle plus limit of 2 weeks to recover) as evidenced by a return to Grade ≤ 1 toxicity level. Patients who experience DLT in the previous cycle should have their dose modified. DLT is defined as an non-hematological event Grade ≥ 3 toxicity or hematological event of Grade 4 toxicity thought to be related to the study medication. Patients who experience DLT in the first cycle and have no response to therapy are removed from the study.

3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione doses are subsequently escalated to 5, 8, 11, 15, and 20 mg/m²/day to a maximum total daily dose of 40 mg. Patients continue to receive 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione on a 4-week cycle per dose level until one of the off-study criteria are met.

Three patients are enrolled in each cohort. If at least one DLT occurs, three additional patients are added to the cohort at that particular dose level. If two DLTs occur, the MTD, defined as the dose at which fewer than one-third of patients at each dose level experiences DLT has been exceeded and four more patients are treated at the previous dose.

Patients who experience DLT during the first 4-week cycle are removed from the study, except if they have a response to therapy. For patients who have completed their first 4-week cycle of without DLT, but who subsequently experience Grade 3 or 4 hematological and/or nonhematological toxicity, treatment is suspended for a minimum of a week. If the toxicity resolves to <Grade 2 within three weeks, the patient

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is treated at two dose levels lower than the dose that caused the toxicity (or a 50% reduction if the patient was treated at the first or second dose level). Patients in whom Grade 3 or 4 toxicity does not resolve to <Grade 1 within three weeks, or those who have another Grade 3 toxicity at the reduced dose are removed from the study.

Pharmacokinetic sampling is performed prior the first dose of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Day 1) and 0.5, 1, 2, 4, 6, 8, 24, and 48 hours thereafter. Sampling is also conducted pre-dose on Days 7 and 21 and 0.5, 1, 2, 4, 6, 8, and 24 post-dose on Day 21 to evaluate steady-state 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione levels.

6.5.5 Treatment of Metastatic Melanoma

Patients with metastatic melanoma were started on 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revmid™) at 5 mg/day for seven days. The dose was then increased every seven days to 10 mg/day, 25 mg/day, and 50 mg/day, respectively, for a total of four weeks on therapy. Five of the 13 melanoma patients who were treated under this regimen either showed disease stabilization or a partial response in the first four weeks of treatment. Tumor response was seen in cutaneous and subcutaneous lesions (five patients), lymph nodes (two patients), and liver (one patient). The duration of response was approximately six months. The result suggests that the compound appears is a promising new anti-cancer agent and has both antiangiogenic and immunomodulatory properties.

6.5.6 Treatment of Relapsed or Refractory Multiple Myeloma

Patients with relapsed and refractory Dune-Salmon stage III multiple myeloma, who have either failed at least three previous regimens or presented with poor performance status, neutropenia or thrombocytopenia, are treated with up to four cycles of combination of melphalan (50 mg intravenously), an immunomodulatory compound of the invention (about 1 to 150 mg orally daily), and dexamethasone (40 mg/day orally on days 1 to 4) every four to six weeks. Maintenance treatment consisting of daily an immunomodulatory compound of the invention and monthly dexamethasone are continued until the disease progression. The therapy using an immunomodulatory compound of the invention in combination with melphalan and dexamethasone is highly active and generally tolerated in heavily pretreated multiple myeloma patients whose prognosis is otherwise poor.

The embodiments of the invention described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the invention and are encompassed by the appended claims.

What is claimed is:

1. A method of treating non-Hodgkin's lymphoma, which comprises administering to a patient having non-Hodgkin's lymphoma from about 5 to about 50 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof.

2. A method of treating ovarian cancer, which comprises administering to a patient having ovarian cancer from about 5 to about 50 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-

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isoindol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of cisplatin.

3. A method of treating pancreatic cancer, which comprises administering to a patient having pancreatic cancer from about 5 to about 50 mg per day of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of gemcitabine.

4. A method of treating renal cancer, which comprises administering to a patient having renal cancer from about 5 to about 50 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof.

5. A method of treating amyloidosis, which comprises administering to a patient having amyloidosis from about 5 to about 50 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof.

6. A method of treating cutaneous T-Cell lymphoma, which comprises administering to a patient having cutaneous T-Cell lymphoma from about 5 to about 50 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione or a pharmaceutically acceptable salt thereof.

7. A method of treating non-Hodgkin's lymphoma, which comprises administering to a patient having non-Hodgkin's lymphoma from about 5 to about 50 mg per day of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of rituximab.

8. A method of treating ovarian cancer, which comprises administering to a patient having ovarian from about 5 to about 50 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of topotecan.

9. A method of treating non-Hodgkin's lymphoma, which comprises administering to a patient having non-Hodgkin's lymphoma from about 5 to about 50 mg per day of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of fludarabine.

10. A method of treating cutaneous B-Cell lymphoma, which comprises administering to a patient having cutaneous B-Cell lymphoma from about 5 to about 50 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof.

11. A method of treating diffuse large B-Cell lymphoma, which comprises administering to a patient having diffuse large B-Cell lymphoma from about 5 to about 50 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof.

12. The method of claim 5, 6, 10 or 11, which further comprises administering a therapeutically effective amount of rituximab.

13. The method of claim 5, 6, 10 or 11, which further comprises administering a therapeutically effective amount of fludarabine;

14. The method of any one of claims 1 and 2 to 11, wherein the compound is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

15. The method of any one of claims 1 and 2 to 11, wherein the compound is a pharmaceutically acceptable salt.

16. A method of treating amyloidosis, which comprises administering to a patient having amyloidosis from about 5 to about 50 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof.

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dol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of melphalan or dexamethasone.

17. A method of treating non-Hodgkin's lymphoma, which comprises administering to a patient having non-Hodgkin's lymphoma from about 5 to about 50 mg per day of 3-(4-amino-oxo-1,3-dihydro-isindol-2-yl)-piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of a protein kinase inhibitor.

18. The method of any one of claims 1, 2 to 11, 16 or 17, wherein the compound is administered orally.

19. The method of claim 18, wherein the compound is administered in the form of a capsule or tablet.

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20. The method of any one of claims 1, 2 to 11, 16 or 17, wherein the compound is administered in an amount of from about 5 to about 25 mg per day.

21. The method of claim 20, wherein the compound is administered cyclically.

22. The method of claim 21, wherein one cycle comprises four to six weeks.

23. The method of claim 21, wherein one cycle comprises the administration of the compound for 21 days followed by seven days rest.

24. The method of claim 21, wherein the compound is administered in an amount of from about 5 to about 25 mg per day for 21 days followed by seven days rest in a 28 day cycle.

* * * * *

EXHIBIT I



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**(12) United States Patent
Zeldis****(10) Patent No.: US 8,741,929 B2**
(45) Date of Patent: *Jun. 3, 2014**(54) METHODS USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE FOR TREATMENT OF MANTLE CELL LYMPHOMAS****(75) Inventor: Jerome B. Zeldis**, Princeton, NJ (US)**(73) Assignee: Celgene Corporation**, Summit, NJ (US)**(*) Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 220 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: 12/621,502**(22) Filed: Nov. 19, 2009****(65) Prior Publication Data**

US 2010/0068206 A1 Mar. 18, 2010

Related U.S. Application Data**(63)** Continuation of application No. 11/888,881, filed on Aug. 1, 2007, now abandoned.**(60)** Provisional application No. 60/835,752, filed on Aug. 3, 2006.**(51) Int. Cl.**
A61K 31/445 (2006.01)**(52) U.S. Cl.**
USPC **514/323****(58) Field of Classification Search**

None

See application file for complete search history.

(56) References Cited**U.S. PATENT DOCUMENTS**

3,536,809 A 10/1970 Applezweig
 3,598,123 A 8/1971 Zaffaroni et al.
 3,845,770 A 11/1974 Theeuwes et al.
 3,916,899 A 11/1975 Theeuwes et al.
 4,008,719 A 2/1977 Theeuwes et al.
 4,810,643 A 3/1989 Souza
 4,999,291 A 3/1991 Souza
 5,059,595 A 10/1991 Le Grazie
 5,073,543 A 12/1991 Marshall et al.
 5,120,548 A 6/1992 McClelland et al.
 5,134,127 A 7/1992 Stella et al.
 5,229,496 A 7/1993 Deeley et al.
 5,354,556 A 10/1994 Sparks et al.
 5,385,901 A 1/1995 Kaplan et al.
 5,391,485 A 2/1995 Deeley et al.
 5,393,870 A 2/1995 Deeley et al.
 5,528,823 A 6/1996 Rudy, Jr. et al.
 5,580,755 A 12/1996 Souza
 5,591,767 A 1/1997 Mohr et al.
 5,593,990 A 1/1997 D'Amato
 5,629,327 A 5/1997 D'Amato
 5,635,517 A 6/1997 Muller et al.
 5,639,476 A 6/1997 Oshlack et al.
 5,674,533 A 10/1997 Santus et al.
 5,698,579 A 12/1997 Muller
 5,712,291 A 1/1998 D'Amato
 5,731,325 A 3/1998 Andrulis, Jr. et al.

5,733,566 A 3/1998 Lewis
 5,798,368 A 8/1998 Muller et al.
 5,874,448 A 2/1999 Muller et al.
 5,877,200 A 3/1999 Muller
 5,929,117 A 7/1999 Muller et al.
 5,955,476 A 9/1999 Muller et al.
 6,020,358 A 2/2000 Muller et al.
 6,071,948 A 6/2000 D'Amato
 6,114,355 A 9/2000 D'Amato
 6,140,346 A 10/2000 Andrulis, Jr. et al.
 6,228,879 B1 5/2001 Green et al.
 6,235,756 B1 5/2001 D'Amato
 6,281,230 B1 8/2001 Muller et al.
 6,316,471 B1 11/2001 Muller et al.
 6,326,388 B1 12/2001 Man et al.
 6,335,349 B1 1/2002 Muller et al.
 6,380,239 B1 4/2002 Muller et al.
 6,395,754 B1 5/2002 Muller et al.
 6,403,613 B1 6/2002 Man et al.
 6,420,414 B1 7/2002 D'Amato
 6,458,810 B1 10/2002 Muller et al.
 6,469,045 B1 10/2002 D'Amato
 6,476,052 B1 11/2002 Muller et al.
 6,518,298 B2 2/2003 Green et al.
 6,555,554 B2 4/2003 Muller et al.
 6,673,828 B1 1/2004 Green et al.
 7,468,363 B2 12/2008 Zeldis
 2001/0018445 A1 8/2001 Huang et al.
 2001/0056114 A1 12/2001 D'Amato
 2002/0035090 A1 3/2002 Zeldis et al.
 2002/0045643 A1 4/2002 Muller et al.

(Continued)

FOREIGN PATENT DOCUMENTS

JP 2006-514689 5/2006
 WO WO 98/03502 1/1998
 WO WO 98/54170 12/1998
 WO WO 01/70275 9/2001
 WO WO 01/87307 11/2001
 WO WO 02/059106 8/2002
 WO WO 02/064083 8/2002
 WO PCT/US03/11578 10/2003
 WO WO03086373 10/2003
 WO WO 03/097052 11/2003
 WO WO 2004/043377 5/2004

OTHER PUBLICATIONS

Translation of the Official Action from Russian Patent Office, May 31, 2011.

Bartlett et al., "Recent clinical studies of the immunomodulatory drug (IMiD) lenalidomide", British Journal of Cancer, 2005, 93, 613-619.

(Continued)

Primary Examiner — James D Anderson*(74) Attorney, Agent, or Firm* — Jones Day**(57) ABSTRACT**

Methods of treating, preventing or managing mantle cell lymphomas are disclosed. The methods encompass the administration of an immunomodulatory compound of the invention known as Revlimid® or lenalidomide. The invention further relates to methods of treatment using this compound with chemotherapy, radiation therapy, hormonal therapy, biological therapy or immunotherapy. Pharmaceutical compositions and single unit dosage forms suitable for use in the methods of the invention are also disclosed.

24 Claims, No Drawings

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(56)

References Cited

U.S. PATENT DOCUMENTS

2002/0052398	A1	5/2002	D'Amato
2002/0054899	A1	5/2002	Zeldis
2002/0061923	A1	5/2002	D'Amato
2002/0128228	A1	9/2002	Hwu
2002/0161023	A1	10/2002	D'Amato
2002/0173658	A1	11/2002	Muller et al.
2002/0183360	A1	12/2002	Muller et al.
2003/0013739	A1	1/2003	Masferrer et al.
2003/0028028	A1	2/2003	Man et al.
2003/0045552	A1	3/2003	Robarge et al.
2003/0069428	A1	4/2003	Muller et al.
2003/0096841	A1	5/2003	Robarge et al.
2003/0139451	A1	7/2003	Shah et al.
2003/0144325	A1	7/2003	Muller et al.
2003/0181428	A1	9/2003	Green et al.
2003/0187024	A1	10/2003	D'Amato
2003/0191098	A1	10/2003	D'Amato
2003/0235909	A1	12/2003	Hariri et al.
2004/0029832	A1	2/2004	Zeldis
2004/0077685	A1	4/2004	Figg et al.
2004/0077686	A1	4/2004	Dannenberg et al.
2004/0087546	A1	5/2004	Zeldis
2004/0091455	A1	5/2004	Zeldis
2004/0122052	A1	6/2004	Muller et al.
2004/0266809	A1	12/2004	Emanuel et al.
2010/0196369	A1	8/2010	Zeldis

OTHER PUBLICATIONS

- Thomas E. Witzig, "Current Treatment Approaches for Mantle-Cell Lymphoma", *Journal of Clinical Oncology*, 2005, 23, 26, 6409-6414.
- Carstensen, 1995, *Drug Stability: Principles & Practice*, 2nd ed., Marcel Dekker, New York, NY pp. 379-380.
- Corral et al., 1999, "Immunomodulation by thalidomide and thalidomide analogues," *Ann. Rheum. Dis.* 58(Suppl 1):1107-1113.
- Craig et al., 1967, "Potential anticancer agents. III. 2-phthalimidooaldehydes and derivatives," *Potential Anticancer Agents III* 10:1071-1073.
- Crane, et al., "Immunomodulatory Drugs," *Cancer Investigation*, 2005, 23:625-634.
- Cunningham et al., "Phase II Trial for Lenalidomide Alone in Relapsed/Refractory Aggressive Non-Hodgkin Lymphoma," *Clinical Lymphoma & Myeloma*, 2007, 7(5):339.
- D'Amato et al., 2001, "Mechanism of action of thalidomide and 3-aminothalidomide in multiple myeloma," *Semin Oncol.* 28:597-601.
- D'Amato et al., 1994, "Thalidomide is an Inhibitor of Angiogenesis", *Proc. Natl. Acad. Sci.* 91:4082-4085.
- De et al., 1976, "Hansch analysis for some antineoplastic glutarimides," *J. Indian Chem. Soc.* I:III: 825-826.
- De et al., 1976, "Possible antineoplastic agents: III. Synthesis of 6-alkyl-2-[4'-methoxyphthalimido] and 6-alkyl-3-[3'-4'-dimethoxyphenyl] glutarimides," *J. Indian Chem. Soc.* I:III:1122-1125.
- Dredge et al., 2002, "Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects," *Br. J. Cancer* 87(10):1166-1172.
- Folkman et al., 1983, "Angiogenesis inhibition and tumor regression caused by heparin or a heparin fragment in the presence of cortisone," *Science* 221(4612):719-725.
- Gershbein, 1991, "The thalidomide analog, EM 12, enhances 1,2-dimethylhydrazine-induction of rat colon adenocarcinomas," *Cancer Letters* 60: 129-133.
- Grabstald et al., 1965, "Clinical experiences with thalidomide in patients with cancer," *Clinical Pharmacology and Therapeutics* 6:298-302.
- Lentzsch et al., 2003, "Immunomodulatory analogs of thalidomide inhibit growth of Hs Sultan cells and angiogenesis in vivo," *Leukemia* 17(1):41-44.
- Lentzsch et al., 2002, "S-3-amino-phthalimido-glutarimide inhibits angiogenesis and growth of B-cell neoplasias in mice", *Cancer Research* 62:2300-2305.
- Miyachi et al., 1997, "Novel biological response modifiers: phthalimides with tumor necrosis factor-alpha production-regulating activity," *J. Med. Chem.* 40:2858-2865.
- Muller et al., 1999, "Amino-substituted thalidomide analogs: potent inhibitors of TNF-alpha production," *Bioorg. Med. Chem. Lett.* 9(11):1625-1630.
- Muller et al., 1998, "Thalidomide analogs and PDE4 inhibition," *Bioorg. Med. Chem. Lett.* 8(19):2669-2674.
- Muller et al., 1996, "Structural modifications of thalidomide produce analogs with enhanced tumor necrosis factor inhibitory activity," *J. Med. Chem.* 39(17):3238-3240.
- Olson et al., 1965, "Thalidomide (N-phthaloylglutamide) in the treatment of advanced cancer," *Clinical Pharmacology and Therapeutics* 6(3):292-297.
- Penichet et al., 2001, "Antibody-cytokine fusion proteins for the therapy of cancer," *J. Immunol. Methods* 248(1-2):91-101.
- Physician's Desk Reference*, 2002, 56th ed., pp. 1755-1760.
- Raza et al., 2001, "Thalidomide produces transfusion independence in long-standing refractory anemias of patients with myelodysplastic syndromes," *Blood* 98(4):958-965.
- Shah et al., 1999, "Synthesis and enantiomeric separation of 2-phthalimidino-glutaric acid analogues: potent inhibitors of tumor metastasis," *J. Med. Chem.* 42:3014-3017.
- Shibata et al., 1995, "N-alkylphthalimides: structural requirement of thalidomide action on 12-O-tetradecanoylphorbol-13-acetate-induced tumor necrosis factor alpha production by human leukemia HL-60 cells," *Chem. Pharm. Bull.* 43(1):177-179.
- Shimazawa et al., 1999, "Antiangiogenic activity of tumor necrosis factor-alpha production regulators derived from thalidomide," *Biol. Pharm. Bull.* 22(2):224-226.
- Rubin et al., "Principles of Cancer Treatment-1", 12 ONCO IV 1, May 2003.
- Wilens et al., 1977, *Tetrahedron* 33:2725.
- Wilens, 1972, *Tables of Resolving Agents and Optical Resolutions*, E.L. Eliel, ed., Univ. of Notre Dame Press, Notre Dame, IN pp. 268.
- Wolff et al., 1995, *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed., pp. 172-178, 949-982.
- N. Ake Jonsson, 1972, "Chemical Structure and Teratogenic Properties," *Acta Pharm.*, pp. 521-542.
- Alexanian et al., 2004, "VTD (Velcade, thalidomide, dexamethasone) as primary therapy for newly-diagnosed multiple myeloma," *Ant. Soc. Hematol.* 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract #210.
- Anderson, 2000, "Thalidomide: Therapeutic potential in hematologic malignancies," *Seminars in Hematology* 37(1 Supp 3): 1-4.
- Attal et al., 2004, "Maintenance treatment with thalidomide after autologous transplantation for myeloma: First analysis of a prospective randomized study of the Intergroupe Francophone du Myelome (IFM99 02)," *Am. Soc. Hematol.* 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract #535.
- Bernardeschi et al., 2003, *J. Exp. Clin. Cancer Res.* 22(4):129-133.
- Corral et al., 1999, "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha," *J. Immunol.* 163(1):380-386.
- Davies et al., 2001, "Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma," *Blood* 98(1):210-216.
- Dimopoulos et al., 2004, "Primary treatment with pulsed melphalan, dexamethasone, thalidomide (MDT) for symptomatic patients with multiple myeloma ≥75 years of age," *Am. Soc. Hematol.* 46th Ann. Meeting Dec. 4-7, 2004, San Diego, CA Abstract #1482.
- Eisen et al., 2000, "Continuous low dose Thalidomide: a phase II study in advanced melanoma, renal cell, ovarian and breast cancer," *Br. J. Cancer* 82(4):812-817.
- Fakhouri et al., 2004, "Thalidomide in patients with multiple myeloma and renal failure," *Br. J. Haematol.* 125:90-102.
- Fenk et al., 2005, "Single-agent thalidomide for treatment of first relapse following high-dose chemotherapy in patients with multiple myeloma," *Leukemia* 19(1):156-159.
- Gupta et al., 2001, "Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications," *Leukemia* 15(12):1950-1961.

US 8,741,929 B2

Page 3

(56)

References Cited

OTHER PUBLICATIONS

- Haslett et al., 2003, "Thalidomide and a thalidomide analogue drug costimulate virus-specific CD8+ T cells in vitro," *J. Infect. Dis.* 187(6):946-955.
- Hideshima et al., 2000, "Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy," *Blood* 96(9):2943-2950.
- Offidani et al., 2003, Thalidomide plus oral melphalan for advanced multiple myeloma: a phase II study. *Haematologica*. Dec. 2003;88(12):1432-1433.
- Palumbo et al., 2004, "A prospective randomized trial of oral melphalan prednisone, thalidomide (MPT) vs. oral melphalan, prednisone (MP): An interim analysis," *Am. Soc. Hematol. 46th Ann. Meeting* Dec. 4-7, 2004, San Diego, CA Abstract #207.
- Raje et al., 1999, "Thalidomide—a revival story," *N. Engl. J. Med.* 341(21):1606-1609.
- Rajkumar et al., 2004, "Thalidomide plus dexamethasone versus dexamethasone alone in newly diagnosed multiple myeloma (E1A00): Results of a phase III trial coordinated by the Eastern Cooperative Oncology Group," *Am. Soc. Hematol. 46th Ann. Meeting* Dec. 4-7, 2004, San Diego, CA Abstract #205.
- Rajkumar et al., 2000, "Prognostic value of bone marrow angiogenesis in multiple myeloma," *Clin. Cancer Res.* 6(8):3111-3116.
- Ribatti et al., 1999, "Bone marrow angiogenesis and mast cell density increase simultaneously with progression of human multiple myeloma," *Br. J. Cancer* 79(3-4):451-455.
- Singhal et al., 1999, Antitumor activity of thalidomide in refractory multiple myeloma, *N. Engl. J. Med.* 341(21):1565-1571.
- Steins et al., 2002, "Efficacy and safety of thalidomide in patients with acute myeloid leukemia," *Blood* 99(3):834-839.
- Vacca et al., 1999, "Bone marrow neovascularization, plasma cell angiogenic potential, and matrix metalloproteinase-2 secretion parallel progression of human multiple myeloma," *Blood* 93(9):3064-3073.
- Wohrer et al., 2004, "Effective treatment of primary plasma cell leukemia with thalidomide and dexamethasone—a case report," *Hematol. J.* 5(4):361-363.
- Bach, 1963, "Thalidomide in Cancer Chemotherapy," *The Lancet*, No. 1271, p. 71.
- Bach, 1963, "Studies on the Possible Anti-Neoplastic Effect of Thalidomide," *Acta Pathologica Et Microbiologica Scandinavica* 59:491-499.
- Chaudhry, 1966, *Cancer Research*, "Effect of Prednisolone and Thalidomide on Induced Submandibular Gland Tumors in Hamster," 26(part 1):1884-86.
- DiPaolo, 1963, "Effect of Thalidomide on a Variety of Transplantable Tumors," *Cancer Chemotherapy Reports* No. 29, p. 99-102.
- DiPaolo, 1963, "In vitro Test Systems for Cancer Chemotherapy, II. Correlation of in vitro Inhibition of Dehydrogenase and Growth with in vivo Inhibition of Ehrlich Ascites Tumor," *Proceedings of the Society for Experimental Biology & Medicine*, 114:384-387.
- DiPaolo, 1964, "Thalidomide: Effects on Ehrlich Ascites Tumor Cells in vitro" *Science* 144:1583.
- Mauad, 1963, "Clinical Improvements Obtained in Advanced Cancer Patients with Treatment with Thalidomide Associated with Hormones," *Anais Paulistas de Medicina e Cirurgia* 86:13-40.
- Roe and Mitchley, 1963, "Thalidomide and Neoplasia" *Nature* 200:1016-1017.
- Liu et al., "Phase I study of CC-5013 (Revimid), a thalidomide derivative, in patients with refractory metastatic cancer," *American Society of Clinical Oncology, Abstract #927*, 2003.
- Zangari et al., "Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapse after high dose chemotherapy (IIDCT)," *American Society of Hematology, Abstract #3226*, 2001.
- Zeldis et al., "Update on the evolution of the IMiD™," *International Society for Biological Therapy of Cancer, Oral Abstract*, 2003.
- Anderson, "Moving disease biology from the laboratory to the clinic," *Seminars in Oncology*, 2002 29:17-20.
- Barlogie et al., "Total Therapy II (TTII) for newly diagnosed multiple myeloma (MM): preliminary data on feasibility and efficacy in the first 231 enrolled patients; comparison with predecessor trial total therapy I (TTI) (N=231)," *Blood, Abstract # 2857*, Dec. 7-11, 2001, American Society of Hematology.
- Barlogie et al., "High-dose therapy immunomodulatory drugs in multiple myeloma," *Seminars in Oncology*, 2002, 29 (6):26-33.
- Barlogie et al., "Introduction: Thalidomide and the IMiDs in multiple myeloma," *Seminars in Hematology*, 2003, 40 (4):1-2.
- Barlogie, "Thalidomide and CC-5013 in Multiple Myeloma: The University of Arkansas experience," *Seminars in Hematology*, 2003, 40 (4):33-38.
- Bartlett et al., "The evolution of thalidomide and its IMiD derivatives as anticancer agents," *Nature Reviews Cancer*, 2004, 4 (4):1-9.
- Bartlett et al., "Phase I study to determine the safety, tolerability and immunostimulatory activity of thalidomide analogue CC-5013 in patients with metastatic malignant melanoma and other advanced cancers," *British Journal of Cancer*, 2004, 90:955-961.
- Battegay, "Angiogenesis: mechanistic insights, neovascular diseases, and therapeutic prospects," *J. Mol. Med.*, 1995, 73:333-346.
- Baz et al., "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and revlimid (R) (DvD-R) results in a high response rate in patients with refractory multiple myeloma (RMM)," *Blood, Abstract # 2559*, American Society of Hematology, Dec. 10-13, 2005.
- Brennen et al., "Thalidomide and analogues: current proposed mechanisms and therapeutic usage," *Clinical Prostate Cancer*, 2004, 3 (1):54-61.
- Celgene Corporation, "Celgene advances immunomodulatory drug (IMiD™) clinical program," *Press Release*, Feb. 2000.
- Celgene Corporation, "Initial Phase I solid tumor data on Celgene's lead IMiD™, Revimid™," *Press Release*, Jun. 2001.
- Celgene Corporation, "Celgene Corporation receives orphan drug designation for Revimid™ for multiple myeloma," *Press Release*, Oct. 2001.
- Celgene Corporation, "Celgene Corporation announces third quarter results. Thalomid® (thalidomide) sales increase 24%. Prescriptions up 50%. Enhanced S.T.E.P.S.® launched. Pilot d-MPH data presented," *Press Release*, Oct. 2001.
- Celgene Corporation, "Celgene expands clinical development program for Revimid™. Five additional trials of Revimid initiated in hematological and solid tumor cancers," *Press Release*, Jun. 2002.
- Celgene Corporation, "Celgene Corporation announces third quarter results. Thalomid® (thalidomide) revenue increases 41% to \$30.5 million. Pivotal programs for Thalomid and Revimid™ finalized. Peer-reviewed publications of Thalomid and Revimid data. First JNK inhibitor advanced to Phase I clinical trial," *Press Release*, Oct. 2002.
- Celgene Corporation, "Blood reports Revimid™ has anti-tumor activity in patients with relapsed and refractory multiple myeloma," *Press Release*, Nov. 1, 2002.
- Celgene Corporation, "Celgene provides update on clinical pipeline. Celgene Announces first target indication for Actimid™, CC-8490. SelCID™ program to advance based on results from Phase I/II trial of CC-1088. First JNK inhibitor successfully completes phase I trial," *Press Release*, Jan. 2003.
- Celgene Corporation, "Celgene Corporation announces fourth quarter and full year results for 2002," *Press Release*, Jan. 2003.
- Celgene Corporation, "Celgene receives fast track status from FDA for Revimid™ in multiple myeloma," *Press Release*, Feb. 2003.
- Celgene Corporation, "Celgene receives fast track status from FDA for Revimid™ in myelodysplastic syndromes," *Press Release*, Apr. 2003.
- Celgene Corporation, "New Revimid™ clinical data shows potential as novel approach to treating myelodysplastic syndromes (MDS)," *Press Release*, May 2003.
- Celgene Corporation, "Celgene corporation reports strong operating performance in second quarter as total sales increase 100 percent and profits rise," *Press Release*, Jul. 2003.
- Celgene Corporation, "Celgene corporation reports record operating performance in third quarter as total revenue increases 117% and profits rise," *Press Release*, Oct. 2003.

(56) **References Cited**

OTHER PUBLICATIONS

- Celgene Corporation, "Celgene corporation advances Actimid™ (CC-4047) into phase II trial for prostate cancer," Press Release, Oct. 2003.
- Celgene Corporation, "Additional clinical data presented on Revimid™ in myelodysplastic syndromes at the American Society of Hematology 45th annual meeting," Press Release, Dec. 2003.
- Celgene Corporation, "Celgene corporation reviews 2003 achievements and announces 2004 financial outlook," Press Release, Jan. 2004.
- Celgene Corporation, "Revlimid™ receives orphan drug designation from the European commission for multiple myeloma," Press Release, Feb. 2004.
- Celgene Corporation, "Revlimid™ receives orphan drug designation from the European commission for myelodysplastic syndromes," Press Release, Mar. 2004.
- Celgene Corporation, "Celgene corporation reports record operating performance in first quarter with strong revenue growth and profits," Press Release, Apr. 2004.
- Celgene Corporation, "Celgene announces plans to stop phase III trials in melanoma due to lack of efficacy," Press Release, Apr. 2004.
- Dalgleish, et al., "New thalidomide analogues; anti-cancer, anti-angiogenic and immunostimulatory," *British Journal of Cancer*, 2001, 85 (1)25.
- Dalgleish et al., "Thalidomide analogues CC-5013 and CC-4047 induce T cell activation and IL-12 production in patients with both solid tumours and relapsed and refractory multiple myeloma," *British Journal of Cancer*, 2003, 88(Suppl 1), S25-S54.
- Database Pharmaml XP002369094 retrieved from STN. Database accession No. 1659300, & Marketletter, Oct. 9, 2001.
- Database NLDB XP002369095 retrieved from STN. Database accession No. 2002:35280, & Marketletter, Jun. 18, 2001.
- Davies et al., "Thalidomide (Thal) and immunomodulatory derivatives (IMiDs) augment natural killer (NK) cell cytotoxicity in multiple myeloma(MM)," Abstract # 3617, American Society of Hematology, Dec. 1-5, 2000.
- Davies et al., "Thalidomide (Thal) and immunomodulatory derivatives (IMiDs) augment natural killer (NK) cell cytotoxicity in multiple myeloma ~MM)," Abstract # P222, VIIIth International Myeloma Workshop, May 4-8, 2001.
- Dibbs et al., "Thalidomide and thalidomide analogs suppress TNF γ secretion by myocytes," Abstract # 1284, *Circulation*, 1998.
- Dimopoulos et al., "Results of thalidomide and IMiDs in multiple myeloma," Abstract # P12.1.4, International Multiple Myeloma Workshop, May 23-27, 2003.
- Dimopoulos et al., "Treatment of plasma cell dyscrasias with thalidomide and its derivatives," *Journal of Clinical Oncology*, Dec. 1, 2003, 21 (23)4444-4454.
- Dimopoulos et al., "Study of lenalidomide plus dexamethasone versus dexamethasone alone in relapsed or refractory multiple myeloma (MM): Results of a phase 3 Study (MM-010)," Abstract # 6, American Society of Hematology, Dec. 10-13, 2005.
- Dredge et al., "A costimulatory thalidomide analog enhances the partial anti-tumor immunity of an autologous vaccination in a model of colorectal cancer," Abstract # 491, American Association for Cancer Research, Apr. 6-10, 2002.
- Dredge et al., "Adjuvants and the promotion of Th1-type cytokines in tumour immunotherapy," *Cancer Immunol. Immunother.*, 2002, 51:521-531.
- Dredge et al., "Immunological effects of thalidomide and its chemical and functional analogs," *Critical Reviews in Immunology*, 2002, 22 (5&6):425-437.
- Dredge et al., "Protective antitumor immunity induced by a costimulatory thalidomide analog in conjunction with whole tumor cell vaccination is mediated by increased Th1-type immunity1," *The Journal of Immunology*, 2002, 168:4914-4919.
- Dredge et al., "Recent developments in antiangiogenic therapy," *Expert Opin. Biol. Ther.*, 2002, 2 (8):953-966.
- Dredge et al., "Angiogenesis inhibitors in cancer therapy," *Current Opinion in Investigational Drugs*, 2003, 4 (6):667-674.
- Dredge et al., "Thalidomide analogs as emerging anti-cancer drugs," *Anti-Cancer Drugs*, 2003, 14:331-335.
- Fickentscher et al., "Stereochemical properties and teratogenic activity of some tetrahydrophthalimides," *Molecular Pharmacology*, 1976, 13:133-141.
- Figg et al., "Inhibition of angiogenesis: treatment options for patients with metastatic prostate cancer," *Investigational New Drugs*, 2002, 20(2):183-194.
- Galustian et al., "Thalidomide-derived immunomodulatory drugs as therapeutic agents," *Expert Opin. Biol. Ther.*, 2004, 4 (12):1-8.
- Glaspy et al., "The potential role of thalidomide and thalidomide analogs in melanoma," *Clinical Advances in Hematology & Oncology*, 2004, 1-7.
- Goy, "Mantle Cell Lymphoma: Evolving Novel Options," *Current Oncology Reports*, 2007, 9(5):391-398.
- Gupta et al., "Adherence of multiple myeloma cells to bone marrow stromal cells upregulates vascular endothelial growth factor secretion: therapeutic applications," *Leukemia*, 2001, 15:1950-1961.
- Hayashi et al., "Mechanisms whereby immunomodulatory analogs of thalidomide augment autologous NK cell anti-myeloma immunity," *Blood*, Abstract #3219, Dec. 6-10, 2002, American Society of Hematology.
- He, W., et al., 1993, Abstract of papers, 206th American Chemical Society, Chicago, IL; *Med. Chem.*, paper 216.
- Helm et al., "Comparative teratological investigation of compounds of structurally and pharmacologically related to thalidomide," *Arzneimittel Forschung/Drug Research*, 1981, 31 (I)941-949.
- Hernandez-Ilizaliturri et al., "Addition of immunomodulatory drugs CC5013 or CC4047 to rituximab enhances anti-tumor activity in a severe combined immunodeficiency (SCID) mouse lymphoma model," Abstract # 235, American Society of Hematology, Dec. 6-9, 2003.
- Hernandez-Ilizaliturri, et al., "Immunomodulatory Drug CC-5013 or CC-4047 and Rituximab Enhance Antitumor Activity in a Severe Combined Immunodeficient Mouse Lymphoma Model," *Clinical Cancer Research*, 11(16):5984-5992, 2005.
- Hideshima et al., "Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy," *Blood*, 2000, 96:2943-2950, American Society of Hematology.
- Hideshima et al., "Thalidomide (Thal) and its analogs overcome drug resistance of human multiple myeloma (MM) cells to conventional therapy," Abstract 1313, American Society of Hematology, Dec. 1-5, 2000.
- Hunt et al., "Markers of endothelial and haemostatic activation in the use of CC-4047, a structural analogue of thalidamide, in relapsed myeloma," *Blood*, Abstract # 3216, Dec. 6-10, 2002, American Society of Hematology.
- Hussein et al., "Doxil (D), vincristine (V), reduced frequency dexamethasone (d) and Revlimid (DVD-R) a phase I/II trial in advanced relapsed/refractory multiple myeloma (Rmm) patients," *Blood*, Abstract #208, American Society of Hematology, Dec. 4-7, 2004.
- Hwu et al., "Thalidomide and its analogues in the treatment of metastatic melanoma," *Chemotherapy Foundation Symposium*, Abstract #44, 2002.
- Kyle, "Current therapy of multiple myeloma," *Internal Medicine*, 2002, 41 (3)175-180.
- Kyle et al., "Multiple myeloma," *New England Journal of Medicine*, 2004, 351:1860-1873.
- Leblanc et al., "Immunomodulatory drug costimulates T cells via the B7-CD28 pathway," *Blood*, 2004, 103:1787-1790, American Society of Hematology.
- Lentzsch et al., "In vivo activity of thalidomide and immunomodulatory drugs against multiple myeloma," VIIIth International Myeloma Workshop, Abstract #P225, May 4-8, 2001.
- Lentzsch et al., "Immunomodulatory derivative of thalidomide (IMiD CC-4047) determine the lineage commitment of hematopoietic progenitors by down regulation of GATA-1 and modulation of cytokine secretion," Abstract # 3073, American Society of Hematology, Dec. 6-9, 2003.

(56)

References Cited**OTHER PUBLICATIONS**

- Lentzsch et al., "Immunomodulatory derivative of thalidomide (IMiD CC-4047) down regulates CAAT/enhancer-binding protein γ (C/EBP γ) in multiple myeloma (MM)," Abstract # 3456, American Society of Hematology, Dec. 6-9, 2003.
- Luzzio et al., "Thalidomide analogues: derivatives of an orphan drug with diverse biological activity," *Expert Opin. Ther. Patents*, 2004, 14 (2):215-229.
- Man et al., "Fluoro-substituted thalidomide analogues," *Bioorganic & Medicinal Chemistry Letters* 13, 2003, 3415-3417.
- Marriott et al., "Immunotherapeutic and antitumor potential of thalidomide analogues," *Expert Opin. Biol. Ther.*, 2001, 1 (4):1-8.
- Marriott et al., "New thalidomide analogues; anti-cancer, anti-angiogenic and immunostimulatory," *British Journal of Cancer*, 85:25, Jul. 6, 2001.
- Marriott et al., "Thalidomide and its analogues have distinct and opposing effects on TNF- γ and TNFR2 during co-stimulation of both CD4+ and CD8+ T cells," *Clin. Exp. Immunol.*, 2002, 130:75-84.
- Marriott et al., "A novel subclass of thalidomide analogue with anti-solid tumor activity in which caspase-dependent apoptosis is associated with altered expression of bcl-2 family proteins," *Cancer Research*, 2003, 63:593-599.
- Marriott et al., "Thalidomide derived immunomodulatory drugs (IMiDs) as potential therapeutic agents," *Current Drug Targets—Immune, Endocrine & Metabolic Disorders*, 2003, 3:181-186.
- Masellis et al., "Changes in gene expression in bone marrow mesenchymal progenitor cells as a consequence of IMiD therapy in multiple myeloma patients," *Blood*, Abstract # 1548, Dec. 7-11, 2001, American Society of Hematology.
- McCarty, "Thalidomide may impede cell migration in primates by down-regulating integrin γ -chains: potential therapeutic utility in solid malignancies, proliferative retinopathy, inflammatory disorders, neointimal hyperplasia, and osteoporosis," *Medical Hypotheses*, 1997, 49:123-131.
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs (ImiDs) in human multiple myeloma cells: therapeutic implications," Abstract # 3224, Dec. 7-11, 2001, American Society of Hematology.
- Mitsiades et al., "Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications," *Blood*, 2002, 99:4525-4530, American Society of Hematology.
- Mitsiades et al., "CC-5013 Celgene," *Current Opinion in Investigational Drugs*, 2004, 5 (6):635-647.
- Moutouh et al., "Novel immunomodulatory drugs (IMiDs®): A potential, new therapy for γ -hemoglobinopathies," Abstract # 3740, American Society of Hematology, Dec. 4-7, 2004.
- Patten et al., "The early use of the serum free light chain assay in patients with relapsed refractory myeloma receiving treatment with a thalidomide analogue (CC-4047)," Abstract # 1640, American Society of Hematology, Dec. 6-9, 2003.
- Payvandi et al., "Effects of a thalidomide analog on binding activity of transcription factors and cell cycle progression of multiple myeloma cell lines," *Blood*, Abstract #2487, Dec. 1-5, 2000, American Society of Hematology.
- Payvandi et al., "The thalidomide analogs IMiDs enhance expression of CD69 stimulatory receptor on natural killer cells," Abstract # 1793, American Association for Cancer Research, Mar. 24-28, 2001.
- Payvandi et al., "Thalidomide analogs IMiDs inhibit expression of cyclooxygenase-2 in multiple myeloma cell line and LPS stimulated PBMCs," *Blood*, Abstract # 2689, Dec. 7-11, 2001, American Society of Hematology.
- Payvandi et al., "Thalidomide and IMiDs inhibit microvessel formation from human arterial rings in the absence of human liver microsomes," *Blood*, Abstract # 5046, Dec. 6-10, 2002, American Society of Hematology.
- Payvandi et al., "CC-5013 inhibits the expression of adhesion molecules ICAM-1 and CD44 and prevents metastasis of B16 F10 mouse melanoma cells in an animal model," *American Society of Clinical Oncology*, Abstract # 992, 2003.
- Payvandi et al., "Immunomodulatory drugs inhibit expression of cyclooxygenase-2 from TNF- γ , IL-1 γ , and LPS-stimulated human PBMC in a partially IL-10-dependent manner," *Cellular Immunology*, 2004, 81-88.
- Raje et al., "Combination of the mTOR inhibitor rapamycin and CC-5013 has synergistic activity in multiple myeloma," *Blood*, Dec. 15, 2004, 104 (13):4188-4193.
- Rajkumar et al., "Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma," *Blood*, Dec. 15, 2005, 106 (13):4050-4053.
- Richardson et al., "A Phase 1 study of oral CC5013, an immunomodulatory thalidomide (Thal) derivative, in patients with relapsed and refractory multiple myeloma (MM)," *Blood*, Abstract #3225, Dec. 7-11, 2001, American Society of Hematology.
- Richardson et al., "Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma," *Blood*, 2002 100:3063-3067, American Society of Hematology.
- Richardson et al., "A multi-center, randomized, phase 2 study to evaluate the efficacy and safety of 2 CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM)," *Blood*, Abstract #825, American Society of Hematology, Dec. 6-9, 2003.
- Richardson et al., "Immunomodulatory analogs of thalidomide: an emerging new therapy in myeloma," *Journal of Clinical Oncology*, 2004, 22(16):3212-3214.
- Richardson et al., "A multicenter, single-arm, open-label study to evaluate the efficacy and safety of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma; preliminary results," 10th International Myeloma Workshop, Apr. 10-14, 2005.
- Richardson et al., "Novel biological therapies for the treatment of multiple myeloma," *Best Practice & Research Clinical Haematology*, 2005, 18 (4):619-634.
- Richardson et al., "A phase 1 trial of lenalidomide (Revlimid®) with bortezomib (Velcade®) in relapsed and refractory multiple myeloma," *Blood*, Abstract # 365, American Society of Hematology, Dec. 10-13, 2005.
- Kaufmann et al., "Antitumor activity of rituximab plus thalidomide in patients with relapsed/refractory mantle cell lymphoma," *Blood*, Oct. 15, 2004, 104(8):2269-2271.
- Schafer et al., "Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs," *Journal of Pharmacology and Experimental Therapeutics*, 2003, 305(3):1222-1232.
- Schey et al., "A phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma," *Journal of Clinical Oncology*, 2004, 22 (16):1-8.
- Schey et al., "A phase I study of an immunomodulatory thalidomide analogue (CC4047) in relapse/refractory multiple myeloma," *International Society for Experimental Hematology*, Abstract #248, 2002.
- Shaughnessy et al., "Global gene expression analysis shows loss of C-MYC and IL-6 receptor gene mRNA after exposure of myeloma to thalidomide and IMiD," Abstract # 2485, The American Society of Hematology, Dec. 1-5, 2000.
- Shire et al., "TNF- γ inhibitors and rheumatoid arthritis," *Exp. Opin. Ther. Patents*, 1998, 8 (5):531-544.
- Sorbera et al., "CC-5013. Treatment of multiple myeloma. Treatment of melanoma. Treatment of myelodysplastic syndrome. Angiogenesis inhibitor. TNF- γ production inhibitor," *Drugs of the Future*, 2003, 28(5):425-431.
- Streetly et al., "Thalidomide analogue CC-4047 is effective in the treatment of patients with relapsed and refractory multiple myeloma (MM) and induces T-cell activation and IL-12 production," Abstract # 367, International Multiple Myeloma Workshop, May 23-27, 2003.
- Streetly et al., "Changes in neutrophil phenotype following the administration of CC-4047 (Actimid) to patients with multiple myeloma," Abstract # 2543, American Society of Hematology, Dec. 6-9, 2003.
- Streetly et al., "An update of the use and outcomes of the new immunomodulatory agent CC-4047 (Actimid) in patients with relapsed/refractory myeloma," Abstract #829, American Society of Hematology, Dec. 6-9, 2003.

(56)

References Cited**OTHER PUBLICATIONS**

- Teo et al., "A phase I, single-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacokinetic study of CDC-501, a novel immunomodulatory—oncologic agent, in healthy male subjects with a comparison of fed and fasted," *Clinical Pharmacology and Therapeutics*, 2002, 71 (2)93.
- Teo et al., "Chiral inversion of the second generation IMiD™ CC-4047 (Actimid™) in human plasma and phosphate-buffered saline," *Chirality*, 2003, 15:348-351.
- Thertulien et al., "Hybrid MEL/DT PACE autotransplant regimen for Multiple Myeloma (MM)—safety and efficacy data in pilot study of 15 patients," *Blood*, Abstract # 2869, American Society of Hematology, Dec. 7-11, 2001.
- Toiinya et al., "A phase I study of oral CC-5013 (lenalidomide, Revlimid™), a thalidomide derivative, in patients with refractory metastatic cancer," *Clinical Prostate Cancer*, 2004, 2:241-243.
- Tricot et al., "Angiochemotherapy (ACT) for multiple myeloma (MM) with DT-PACE results in a high response rate, but in contrast to tandem transplants with melphalan does not affect durable disease control," *Blood*, Abstract #3531, American Society of Hematology, Dec. 7-11, 2001.
- Tsenova et al., "Use of IMiD3, a thalidomide analog, as an adjunct to therapy for experimental tuberculous meningitis," *Antimicrobial Agents and Chemotherapy*, 2002, 46 (6)1887-1895.
- Weber, "Lenalidomide (CC-5013, Revlimid™) and other IMiDs," Abstract # PL5.02, International Multiple Myeloma Workshop, Apr. 10-14, 2005.
- Weber et al., "A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma," Abstract # PO.738, International Multiple Myeloma Workshop, Apr. 10-14, 2005.
- Ye et al., "Novel IMiD drugs enhance expansion and regulate differentiation of human cord blood CD34+ cells with cytokines," *Blood*, Abstract #4099, American Society of Hematology, Dec. 6-10, 2002.
- Zangari et al., "Risk factors for deep vein thrombosis (DVT) in a large group of myeloma patients (Pts) treated with thalidomide (Thal): The Arkansas Experience," *Blood*, Abstract # 681, American Society of Hematology, Dec. 7-11, 2001.
- Zangari et al., "Revimid 25 mg (REV 25) × 20 versus 50 mg (Rev 50) × 10 q 28 days with bridging of 5 mg × 10 versus 10 mg × 5 as post-transplant salvage therapy for multiple myeloma (MM)," *Blood*, Abstract # 1642, American Society of Hematology, Dec. 6-9, 2003.
- Zeldis et al., "Potential new therapeutics for Waldenström's macroglobulinemia," *Seminars in Oncology*, 2003, 30 (2):275-281.
- Zhang et al., "CC-5079, a novel microtubule and TNF- α inhibitor with anti-angiogenic and antimetastasis activity," Abstract # B012, International Conference on Molecular Targets and Cancer Therapeutics, Nov. 17-21, 2003.
- Anderson, "The Role of Immunomodulatory Drugs in Multiple Myeloma," *Seminars in Hematology*, vol. 40, No. 4, Suppl 4, 2003: pp. 23-32.
- Weber, "Thalidomide and Its Derivatives: New Promise for Multiple Myeloma," *Cancer Control*, vol. 10, No. 5, 375-383, 2003.
- Patt, Yehuda A.; Hassan, Manal M.; Lozano, Richard D.; Ellis, Lee M.; Peterson, J. Andrew; Waugh, Kimberly A.; "Durable Clinical Response of Refractory Hepatocellular Carcinoma to Orally Administered Thalidomide," *American Journal of Clinical Oncology*, 2000, 23:319-321.
- Richardson, Paul; Hideshima, Tem; Anderson, Kenneth; "Thalidomide: The Revival of a Drug with Therapeutic Promise in the Treatment of Cancer," *Principles & Practice of Oncology*, vol. 15, No. 2, 2001.
- Thomas, Melodie; Doss, Deborah, "Thalidomide Nursing Roundtable Update," *Monograph*, Sep. 2002.
- Richardson, Paul; Hideshima, Tem; Anderson, Kenneth; "Thalidomide: Emerging Role in Cancer Medicine," *Annual Review of Medicine*, 2002, 53:629-657.
- Berenson, J.R.; Bergsagel, P. L.; Munshi, N.; "Initiation and Maintenance of Multiple Myeloma," *Seminars in Hematology*, vol. 36, No. 1, Supp. 3, Jan. 1999, pp. 9-13.
- Gollob, J.A.; Schinipper, C.P.; Orsini, E.; Murphy, E.; Daley, J.F.; Lazo, S.B.; Frank, D.A.; "Characterization of a Novel Subset of CD8 T Cells That Expands in patients Receiving Interleukin-12," *Am. Soc. For Clin. Investigation, Inc.*, vol. 102, No. 3, Aug. 1998, pp. 561-575.
- Cavanagh, L.L.; Barnetson, R.S.; Basten, A.; Halliday, G.M.; "Dendritic Epidermal T-Cell Involvement in Induction of CD8+ T-Cell-Mediated Immunity Against an Ultraviolet Radiation-Induced Skin Tumor," *Int. J. Cancer*: 70, 98-105, 1997.
- Thomas, D.A.; Aguayo, A.; Estey, E.; Albitar, M.; O'Brien, S.; Giles, F.J.; Beran, M.; Cortes, J.; Zeldis, J.; Keating, M.J.; Barlogie, B.; Kantarjian, H.M., "Thalidomide as anti-angiogenesis therapy (rx) in refractory or relapsed leukemia," Abstract #2269, American Society of Hematology, Dec. 3-7, 1999.
- Barlogie, B.; Desikan, R.; Munshi, N.; Siegel, D.; Mehta, J.; Singhal, S.; Anaissie, E., "Single Course D.T. Pace Anti-Angiochemotherapy Effects CR in Plasma Cell Leukemia and Fulminant Multiple Myeloma (MM)," Abstract #4180, American Society of Hematology, Dec. 4-9, 1998.
- Hideshima, T.; Chauhan, D.; Shima, Y.; Noopur, R.; Davies, F.E.; Tai, Y.; Treon, S.P.; Lin, B.K.; Schlossman, R.L.; Richardson, P.G.; Gupta, D.; Muller, G.W.; Stirling, D.I.; Anderson, K.C., "Thalidomide (THAL) and its Analogs Overcome Drug Resistance of Human Multiple Myeloma (MM) Cells to Conventional Therapy," Abstract #1313, American Society of Hematology, Dec. 1-5, 2000.
- Payvandi, F.; Wu, L.; Gupta, D.; Hideshima, T.; Haley, M.; Muller, G.; Chen, R.; Anderson, K.C.; Stirling, D., "Effects of a Thalidomide Analog on Binding Activity of Transcription Factors and Cell Cycle Progression of Multiple Myeloma Cell Lines," Abstract #2487, American Society of Hematology, Dec. 1-5, 2000.
- Davies, F.E.; Raje, N.; Hideshima, T.; Lentzsch, S.; Young, G.; Tai, Y.; Lin, B.K.; Podar, K.; Chauhan, D.; Treon, S.P.; Gupta, D.; Mitsiades, C.; Mitsiades, N.; Hayashi, T.; Richardson, P.G.; Schlossman, R.L.; Muller, G.W.; Stirling, D. I.; Anderson, K.C., "Thalidomide (THAL) and Immunomodulatory Derivatives (IMiDs) Augment Natural Killer (NK) Cell Cytotoxicity in Multiple Myeloma (MM)," Abstract #3617, American Society of Hematology, Dec. 1-5, 2000.
- Hideshima, T.; Chauhan, D.; Castro, A.; Hayashi, T.; Mitsiades, C.; Mitsiades, N.; Akiyama, M.; Richardson, P.G.; Schlossman, R.L.; Adams, J.; Anderson, K.C., NF- κ B as a Therapeutic Target in Multiple Myeloma (MM). Abstract #1581, American Society of Hematology, Dec. 7-11, 2001.
- Lentsch, S.; Rogers, M.; Leblanc, R.; Birsner, A.; Shah, J.; Anderson K.; D'Amato R., "3-Amino-Phthalimido-Glutarimide (S-3APG) Inhibits Angiogenesis and Growth in Drug Resistant Multiple Myeloma (MM) in vivo," Abstract #1976, American Society of Hematology, Dec. 7-11, 2001.
- Park, Y.; Kim, S.A.; Kim, C.J.; Chung, J.H., "Mechanism of the Effect of Thalidomide on Human Multiple Myeloma Cells," Abstract #2685, American Society of Clinical Oncology, May 12-17, 2001.
- Mitsiades, N.; Mitsiades, C.; Poulaiu, V.; Akiyama, M.; Tai, Y.; Lin, B.; Iiyasiii, T.; Catley, L.; Hideshima, T.; Chauhan, D.; Treon, S.P.; Anderson, K.C., "Apoptotic Signaling Induced by Immunomodulatory Thalidomide Analogs (Imids) in Human Multiple Myeloma Cells," *Therapeutic Implications*, Abstract #3224, American Society of Hematology, Dec. 7-11, 2001.
- Richardson, P.G.; Schlossman, R.L.; Hideshima, T.; Davies, F.; Leblanc, R.; Catley, L.; Doss, D.; Kelly, K.A.; McKenney, M.; Mechlowicz, J.; Freeman, A.; Deocampo, R.; Rich, R.; Ryoo, J.; Chauhan, D.; Munshi, N.; Weller, E.; Zeldis, J.; Anderson, K.C., "A Phase I Study of Oral CC5013, an Immunomodulatory Thalidomide (Thal) Derivative, in Patients With Relapsed and Refractory Multiple Myeloma (MM)," Abstract #3225, American Society of Hematology, Dec. 7-11, 2001.
- Zangari, M. Tricot, G.; Zeldis, J.; Eddlemon, P.; Saghaififar, F.; Barlogie, B., "Results of Phase I Study of CC5013, for the Treatment of Multiple Myeloma (MM) Patients Who Relapse After High Dose Chemotherapy (HDCT)," Abstract #3226, American Society of Hematology, Dec. 7-11, 2001.

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(56)

References Cited

OTHER PUBLICATIONS

- Khoury, et al., "Long-Term Follow-Up of Autologous Stem Cell Transplantation in Patients with Diffuse Mantle Cell Lymphoma in First Disease Remission," *Cancer*, Dec. 15, 2003, 98(12):2630-2635.
- Khoury, et al., "Nonablative Allogeneic Stem-Cell Transplantation for Advanced/Recurrent Mantle-Cell Lymphoma," *Journal of Clinical Oncology*, Dec. 2003, 21(23):4407-4412.
- Lefrere et al., "Sequential Chemotherapy by CHOP and DHAP Regimens Followed by High-Dose Therapy With Stem Cell Transplantation Includes a High Rate of Complete Response and Improves Event-Free Survival in Mantle Cell Lymphoma: A Prospective Study," *Leukemia*, 2002, 16:587-593.
- Jaffe et al., "Mantle Cell Lymphoma: Biology, Diagnosis and Management," *Hematology* 1999:319-325.
- Hiddemann et al., "Rituximab plus Chemotherapy in Follicular and Mantle Cell Lymphoma," *Seminars in Oncology*, Suppl 2 Feb. 2003, 30(1):16-20.
- Harris et al., "A Revised European-American Classification of Lymphoid Neoplasms: A Proposal from the International Lymphoma Study Group," *Blood*, Sep. 1994, 84(5):1361-1392.
- Harris et al., "World Health Organization Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues: Report of the Clinical Advisory Committee Meeting," *Journal of Clinical Oncology*, Dec. 1999, 17(12):3835-3849.
- Freedman et al., "High-Dose Chemoradiotherapy and Anti-B-Cell Monoclonal Antibody-Purged Autologous Bone Marrow Transplantation in Mantle-Cell Lymphoma: No Evidence for Long-Term Remission," *Journal of Clinical Oncology*, Jan. 1998, 16(1):13-18.
- Foran et al., "European Phase II Study of Rituximab (Chimerica Anti-CD20 Monoclonal Antibody) for Patients with Newly Diagnosed Mantle-Cell Lymphoma and Previously Treated Mantle-Cell Lymphoma, Immunocytoma, and Small B-Cell Lymphocytic Lymphoma," *Journal of Clinical Oncology*, Jan. 2000, 18(2):317-324.
- Fisher et al., "A Clinical Analysis of Two Indolent Lymphoma Entities: Mantle-Cell Lymphoma and Marginal Zone Lymphoma (Including the Mucosa-Associated Lymphoid Tissue and Monocytoid B-Cell Subcategories): A Southwest Oncology Group Study," *Blood*, Feb. 1995, 85(4):1075-1082.
- Fisher, "Mantle Cell Lymphoma: Prognostic Factors and Treatment Results," *Hematology* 1999:325-328.
- Coiffier, "Which Treatment for Mantle-Cell Lymphoma Patients in 1998?", *Journal of Clinical Oncology*, Jan. 1998, 16(1):3-5.
- Coiffier, "Mantle Cell Lymphoma: New Treatment Possibilities," *Hematology* 1999:329-334.
- Coijen, "Cyclophosphamide/Fludarabine (CF) is Active in the Treatment of Mantle Cell Lymphoma," *Leukemia and Lymphoma*, 2001 42(5):1015-1022.
- Campo, et al., "Mantle-Cell Lymphoma," *Seminars in Hematology*, Apr. 1999, 36(2):115-127.
- Zinzani, et al., "Randomized Trial of Fludarabine Versus Fludarabine and Idarubicin as Frontline Treatment in Patients with Indolent or Mantle-Cell Lymphoma," *Journal of Clinical Oncology*, Feb. 2000, 18(4):773-779.
- Witzig, et al., "Phase I/II Trial of IDEC-Y2B8 Radioimmunotherapy for Treatment of Relapsed or Refractory CD20+ B-Cell Non-Hodgkin's Lymphoma," *Journal of Clinical Oncology*, Dec. 1999, 17(12):3793-3803.
- Weisenburger, et al., "Mantle Cell Lymphoma—an Entity Comes of Age," *Blood*, Jun. 1996, 87(11):4483-4494.
- National Cancer Institute Sponsored Study of Classifications of Non-Hodgkin's Lymphomas. *Cancer*, 1982, 49:2112-2135.
- Seng et al., "Indolent B-Cell Non-Hodgkin's Lymphomas," *Oncology*, Dec. 1997, 11(12):1883-1906.
- Rosenwald et al., "The Proliferation Gene Expression Signature is a Quantitative Integrator of Oncogenic Events that Predicts Survival in Mantle Cell Lymphoma," *Cancer Cell*, Feb. 2003, 3:185-197.
- O'Connor, et al., "Marked Clinical Activity of the Novel Proteasome Inhibitor Bortezomib in Patients with Relapsed Follicular (RL) and Mantle Cell Lymphoma (MCL)," Abstract # 6582, *Journal of Clinical Oncology*, Jul. 2004, 22(14S).
- Goy et al., Update on a Phase (ph) 2 study of Bortezomib in Patients (pts) with Relapsed or Refractory Indolent or Aggressive non-Hodgkin's Lymphomas (NHL), Abstract # 6581, *Journal of Clinical Oncology*, Jul. 2004, 22(14S).
- Dreger et al., "The Impact of Autologous Stem Cell Transplantation on the Prognosis of Mantle Cell Lymphoma: a Joint Analysis of Two Prospective Studies with 46 Patients," *The Hematology Journal*, 2000, 1:87-94.
- Prentice, et al., "Future Directions in Haematology: Beyond Multiple Myeloma," *Acta Haematologica*, 2005, 114(suppl 1):27-32.
- Drach et al., "Treatment of Mantle Cell Lymphoma: a Targeting the Microenvironment," *Expert Rev. Anticancer Ther.*, 2005, 5(3):477-485.
- NewsRx Weekly Reports "Revlimid (thalidomide) clinical results in non-Hodgkin lymphoma presented," *Biotech Business Week*, Jul. 24, 2006, p. 179.
- Episcum Pharm & Med Device News "Preliminary Phase II data demonstrates response to Revlimid in patients with aggressive NHL," *Cancer Drug News*, Jun. 20, 2006.
- Vose et al., "Long Term Results of Radioimmunotherapy with Bexxar/BEAM and Autologous Stem Cell Transplantation (ASCT) for Chemotherapy Resistant Aggressive Non-Hodgkin's Lymphoma (NHL)," Abstract #872, *Blood*, Nov. 2003, 102(11).
- Damaj, G. et al., "Thalidomide therapy induces response in relapsed mantle cell lymphoma," *Leukemia*, vol. 17, pp. 1914-1915 [2003].
- Wilson, Edward A. et al., "Response to thalidomide in chemotherapy-resistant mantle cell lymphoma: A case report", *British Journal of Haematology*, vol. 199, pp. 128-130 [2002].
- Shipp et al., "Non-Hodgkin's Lymphoma" *Cancer Principles & Practice of Oncology*, 5th Edition, vol. 2, Section 3:2165-2220, 1997.
- "Phase II Study of Bortezomib in Patients with Previously Untreated or Relapsed Mantle Cell Lymphoma," National Cancer Institute, accessed at <http://www.cancer.gov/search/viewclinicaltrials.aspx?cdrid=69207&version=healthprofessional>, Oct. 12, 2006.
- Eve et al., "Efficacy and Safety of Conventional-Dose Lenalidomide Followed by Low-Dose Maintenance Lenalidomide for Relapsed/Refractory Mantle Cell Lymphoma (MCL): Results from a UK Phase II Study," *11th Triennial International Conference on Malignant Lymphoma*, Jun. 15-18, 2011, Lugano, Switzerland, Abstract #438.
- Furtado et al., "Lenalidomide Treatment—Safe to Administer to Cytopenic Patients," *11th Triennial International Conference on Malignant Lymphoma*, Jun. 15-18, 2011, Lugano, Switzerland, Abstract #439.
- Morrison, et al., Therapy with Bortezomib + Lenalidomide is Tolerable in Patients (PTS) with Relapsed/Refractory Mantle Cell Lymphoma (MCL): Interim Results of CALGB 50501, *11th Triennial International Conference on Malignant Lymphoma*, Jun. 15-18, 2011, Lugano, Switzerland, Abstract #436.
- Qian, et al., "Lenalidomide synergizes with dexamethasone to induce growth arrest and apoptosis of mantle cell lymphoma cells in vitro and in vivo," *Leukemia Research*, 2011, 35:380-386.
- Gribben, et al., "New Evidence for Mechanism of Action of IMiDs® in Lymphomas, Focus on MCL," *11th Triennial International Conference on Malignant Lymphoma*, Jun. 15-18, 2011, Lugano, Switzerland.
- Hirokazu Murakami et al., "Thalidomide, The past, present and future", *Journal of Clinical and Experimental Medicine*, 2004, 208(13):1039-1044.
- Benefits of Velcade® (bortezomib), printed from www.velcade.com on Nov. 28, 2012.
- Flinn et al., "Rituximab, Lenalidomide, and Bortezomib in the First-Line or Second-Line Treatment of Patients with Mantle Cell Lymphoma a Phase I/II Trial". Submitted to be presented at 54th ASH Annual Meeting and Exposition, Atlanta, Georgia, Dec. 8-11, 2012, Abstract #2748.

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(56)

References Cited

OTHER PUBLICATIONS

Goy et al., "Phase II Multicenter Study of Single-Agent Lenalidomide in Subjects with Mantle Cell Lymphoma Who Relapsed or Progressed After or Were Refractory to Bortezomib: The MCL-001 "Emerge" Study", Submitted to be presented at 54th ASH Annual Meeting and Exposition, Atlanta, Georgia, Dec. 8-11, 2012, Abstract #905.

Kane et al., "Bortezomib for the treatment of mantle cell lymphoma." Clin Cancer Res. 2007 13(18 Pt 1):5291-4.

Zinzani et al., "Phase II Multicenter Study of the Safety and Efficacy of Single-Agent Lenalidomide in Subjects with Relapsed/Refractory Mantle Cell Lymphoma: Long-Term Follow-up Analysis of the NHL-003 Study." Submitted to be presented at 54th ASH Annual

Meeting and Exposition, Atlanta, Georgia, Dec. 8-11, 2012, Abstract #2738.

Final Office Action in corresponding Japanese Patent Application No. 2009-522882 (English translation provided) dated Apr. 16, 2013.

Notice of Preliminary Rejection in corresponding Korean Patent Application No. 10-2009-7004393 (English translation provided) dated Aug. 29, 2013.

Goy, A. et al., "Single-Agent Lenalidomide in Patients With Mantle-Cell Lymphoma Who Relapsed or Progressed After or Were Refractory to Bortezomib: Phase II MCL-001 (Emerge) Study," Journal of Clinical Oncology, published online before print Sep. 3. 2013, doi: 10.1200/JCO.2013.49.2835.

Teo, Steven K., "Properties of Thalidomide and its Analogues: Implications for Anticancer Therapy," *The AAPS Journal*, 2005, 7(1):E14-F19.

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METHODS USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE FOR TREATMENT OF MANTLE CELL LYMPHOMAS

1. CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation application of U.S. non-provisional application Ser. No. 11/888,881, filed Aug. 1, 2007, which claims the benefit of U.S. provisional application 60/835,752, filed Aug. 3, 2006, both of which are incorporated by reference herein in their entirety.

2. FIELD OF THE INVENTION

This invention relates to methods of treating, preventing or managing certain types of lymphomas with an immunomodulatory compound having the chemical name of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, which is also known as or lenalidomide, Revlimid® or Revimid®. In particular, this invention encompasses methods of treating, preventing or managing non-Hodgkin's lymphomas, including but not limited to, mantle cell lymphoma (MCL), lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, and mantle zone lymphoma, using the compound alone as a therapeutic.

The invention also encompasses the use of specific combinations or "cocktails" of Revlimid® and other therapy, e.g., radiation or other chemotherapeutics, including but not limited to, anti-cancer agents, immunosuppressive agents, and anti-inflammatories such as steroids. The invention also relates to pharmaceutical compositions and dosing regimens with said compound alone that is as a therapeutic.

3. BACKGROUND OF THE INVENTION

Cancer is characterized primarily by an increase in the number of abnormal cells derived from a given normal tissue, invasion of adjacent tissues by these abnormal cells, or lymphatic or blood-borne spread of malignant cells to regional lymph nodes and to distant sites (metastasis). Clinical data and molecular biologic studies indicate that cancer is a multistep process that begins with minor preneoplastic changes, which may under certain conditions progress to neoplasia. The neoplastic lesion may evolve clonally and develop an increasing capacity for invasion, growth, metastasis, and heterogeneity, especially under conditions in which the neoplastic cells escape the host's immune surveillance. Roitt, I., Brostoff, J. and Kale, D., *Immunology*, 17.1-17.12 (3rd ed., Mosby, St. Louis, Mo., 1993).

There is an enormous variety of cancers which are described in detail in the medical literature. Examples includes cancer of the blood, lung, colon, rectum, prostate, breast, brain, and intestine. The various forms of the cancers such as lymphomas are described in U.S. provisional application No. 60/380,842, filed May 17, 2002, the entireties of which are incorporated herein by reference (see, e.g., Section 2.2. Types of Cancers).

Lymphoma is a heterogeneous group of neoplasms arising in the reticuloendothelial and lymphatic systems. *The Merck Manual*, 955 (17th ed. 1999). Non-Hodgkin's lymphoma (NHL) refers to malignant monoclonal proliferation of lymphoid cells in the immune system, including lymph nodes, bone marrow, spleen, liver and gastrointestinal (GI) tract. *The Merck Manual*, at 958.

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phoid cells in the immune system, including lymph nodes, bone marrow, spleen, liver and gastrointestinal (GI) tract. *The Merck Manual*, at 958.

Mantle cell lymphoma (MCL) is a distinct entity among the non-Hodgkin's lymphomas. Drach J.; et al., *Expert Review of Anticancer Therapy*, 2005, 5(3), pp. 477-485. In the International Lymphoma Classification Project, MCL accounted for 8% of all non-Hodgkin lymphomas. MCL is recognized in the Revised European-American Lymphoma and World Health Organization classifications as a distinct clinicopathologic entity. MCL was not recognized by previous lymphoma classification schemes; and it was frequently categorized as diffuse small-cleaved cell lymphoma by the International Working Formulation or centrocytic lymphoma by the Kiel classification. *The Merck Manual*, at 958-959.

MCL is a lymphoproliferative disorder derived from a subset of naive pregerminal center cells localized in primary follicles or in the mantle region of secondary follicles. MCL is characterized by a specific chromosomal translocation, the t(11; 14)(q13;q32). Drach J.; et al., *Expert Review of Anticancer Therapy*, 2005, 5(3), pp. 477-485. This translocation involves the immunoglobulin heavy-chain gene on chromosome 14 and the BCL1 locus on chromosome 11. Drach J.; et al., p 477. The molecular consequence of translocation is overexpression of the protein cyclin D1 (coded by the PRAD1 gene located close to the breakpoint). Id. Cyclin D1 plays a key role in cell cycle regulation and progression of cells from G1 phase to S phase by activation of cyclin-dependent kinases. Id.

NHL has been associated with viral infection (Epstein-Barr virus, HIV, human T-lymphotropic virus type 1, human herpesvirus 6), environmental factors (pesticides, hair dyes), and primary and secondary immunodeficiency. No causative factor has been identified for MCL or for most patients with NHL of other types.

MCL has poor clinical outcome and is an incurable lymphoma with limited therapeutic options for patients with relapsed or refractory disease. Drach J.; et al., p. 477. Therefore, a tremendous demand exists for new methods and compositions that can be used to treat patients with MCL.

4. SUMMARY OF THE INVENTION

This invention encompasses methods of treating, preventing or managing certain types of lymphomas, including primary and metastatic cancer, as well as cancers that are relapsed, refractory or resistant to conventional chemotherapy. In particular, methods of this invention encompass methods of treating, preventing or managing various forms of lymphomas such as mantle cell lymphoma, MCL, lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, follicular lymphoma, and mantle zone lymphoma, including lymphomas that are relapsed, refractory or resistant.

The methods comprise administering to a patient in need of such treatment, prevention or management a therapeutically or prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (e.g., hydrate), stereoisomer, clathrate, or prodrug thereof. In a preferred embodiment, the immunomodulatory compound is used alone, that is without other chemotherapeutics.

In another methods of the invention, an immunomodulatory compound of the invention is administered in combination with a therapy conventionally used to treat, prevent or

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manage lymphomas. Examples of such conventional therapies include, but are not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy, immunotherapy and combinations thereof.

This invention also encompasses pharmaceutical compositions, single unit dosage forms, and dosing regimens which comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (e.g., hydrate), stereoisomer, clathrate, or prodrug thereof, and a second, or additional, active agent or ingredient. Second active agents or ingredients include specific combinations, or "cocktails," of drugs or therapy, or both. In certain embodiments, the second active agent is selected from a hematopoietic growth factor, cytokine, anti-cancer agent, antibiotic, cox-2 inhibitor, corticosteroid, rituximab, or a combination thereof. In other embodiments, the second active agent is rituximab, dexamethasone or prednisone.

The preferred compound to be used in the methods and composition is 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®). In some embodiments, the amount of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is from about 5 mg to about 50 mg or from about 5 mg to about 25 mg.

5. DETAILED DESCRIPTION OF THE INVENTION

A first embodiment of the invention encompasses methods of treating, managing, or preventing certain types of lymphomas which comprises administering to a patient in need of such treatment, management or prevention a therapeutically or prophylactically effective amount of an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (e.g., hydrate), stereoisomer, clathrate, or prodrug thereof. In particular, methods of this invention encompass methods of treating, preventing or managing various forms of lymphomas, including but not limited to, mantle cell lymphoma, MCL, lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, follicular lymphoma, and any type of the mantle cell lymphomas that can be seen under the microscope (nodular, diffuse, blastic and mentle zone lymphoma). In one embodiment, the lymphoma is refractory, relapsed, or is resistant to chemotherapy other than an immunomodulatory compound of the invention.

In a separate and distinct embodiment of the invention, the immunomodulatory compound of the invention is administered in combination with another drug ("second active agent or ingredient") or another therapy for treating, managing, or preventing cancer. Second active agents include small molecules and large molecules (e.g., proteins and antibodies), examples of which are provided herein, as well as stem cells or cord blood. Methods, or therapies, that can be used in combination with the administration of an immunomodulatory compound of the invention include, but are not limited to, surgery, blood transfusions, immunotherapy, biological therapy, radiation therapy, and other non-drug based therapies presently used to treat, prevent or manage cancer.

The invention also encompasses pharmaceutical compositions (e.g., single unit dosage forms) that can be used in methods disclosed herein. Particular pharmaceutical compositions comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (e.g.,

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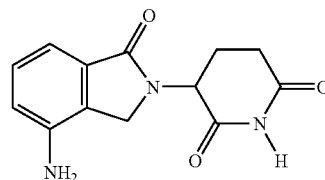
hydrate), stereoisomer, clathrate, or prodrug thereof, and a second active agent or ingredient.

5.1 Immunomodulatory Compounds

Compounds used in the invention include compounds that are racemic, stereomerically enriched or stereomerically pure. In some embodiments, pharmaceutically acceptable salts, solvates (e.g., hydrate), clathrates, and prodrugs thereof are included. Preferred compounds used in the invention are small organic molecules having a molecular weight less than about 1,000 g/mol, and are not proteins, peptides, oligonucleotides, oligosaccharides or other macromolecules.

As used herein and unless otherwise indicated, the terms "immunomodulatory compounds" and "IMiDs®" (Celgene Corporation) encompasses small organic molecules that markedly inhibit TNF- α , LPS induced monocyte IL1 β and IL12, and partially inhibit IL6 production. Specific immunomodulatory compounds of the invention are discussed below.

In the most preferred embodiment, "an immunomodulatory compound of the invention" refers to 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (lenalidomide, also known as Revlimid® or Revimid®). The compound 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione has the following chemical structure:



Specific examples of immunomodulatory compounds, include, but are not limited to, cyano and carboxy derivatives of substituted styrenes such as those disclosed in U.S. Pat. No. 5,929,117; 1-oxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidine-3-yl)isoindolines such as those described in U.S. Pat. No. 5,874,448; the tetra substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolines described in U.S. Pat. No. 5,798,368; 1-oxo and 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)isoindolines, including, but not limited to, those disclosed in U.S. Pat. No. 5,635,517; substituted 2-(2,6-dioxopiperidin-3-yl)phthalimides and substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindoles such as those described in U.S. Pat. Nos. 6,281,230 and 6,316,471; a class of non-polypeptide cyclic amides disclosed in U.S. Pat. Nos. 5,698,579 and 5,877,200; thalidomide analogs, including hydrolysis products, metabolites, and precursors of thalidomide, such as those described in U.S. Pat. Nos. 5,593,990, 5,629,327, and 6,071,948 to D'Amato; and isoindole-imide compounds such as those described in U.S. patent publication no. 2003/0096841, and International Application No. PCT/US01/50401 (International Publication No. WO 02/059106). The entireties of each of the patents and patent applications identified herein are incorporated herein by reference. Immunomodulatory compounds of the invention do not include thalidomide.

The immunomodulatory compounds of the invention can either be commercially purchased or prepared according to the methods described in the patents or patent publications disclosed herein (see e.g., U.S. Pat. No. 5,635,517, incorporated herein by reference). Further, optically pure compounds can be asymmetrically synthesized or resolved using known

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resolving agents or chiral columns as well as other standard synthetic organic chemistry techniques.

As used herein and unless otherwise indicated, the term “pharmaceutically acceptable salt” encompasses non-toxic acid and base addition salts of the compound to which the term refers. Acceptable non-toxic acid addition salts include those derived from organic and inorganic acids or bases known in the art, which include, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric acid, malic acid, maleic acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, embolic acid, enanthic acid, and the like.

Compounds that are acidic in nature are capable of forming salts with various pharmaceutically acceptable bases. The bases that can be used to prepare pharmaceutically acceptable base addition salts of such acidic compounds are those that form non-toxic base addition salts, i.e., salts containing pharmacologically acceptable cations such as, but not limited to, alkali metal or alkaline earth metal salts and the calcium, magnesium, sodium or potassium salts in particular. Suitable organic bases include, but are not limited to, N,N-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), lysine, and procaine.

As used herein and unless otherwise indicated, the term “prodrug” means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide the compound. Examples of prodrugs include, but are not limited to, derivatives of immunomodulatory compounds of the invention that comprise biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Other examples of prodrugs include derivatives of immunomodulatory compounds of the invention that comprise —NO, —NO₂, —ONO, or —ONO₂ moieties. Prodrugs can typically be prepared using well-known methods, such as those described in 1 *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed. 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elsevier, New York 1985).

As used herein and unless otherwise indicated, the terms “biohydrolyzable amide,” “biohydrolyzable ester,” “biohydrolyzable carbamate,” “biohydrolyzable carbonate,” “biohydrolyzable ureide,” “biohydrolyzable phosphate” mean an amide, ester, carbamate, carbonate, ureide, or phosphate, respectively, of a compound that either: 1) does not interfere with the biological activity of the compound but can confer upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is biologically inactive but is converted in vivo to the biologically active compound. Examples of biohydrolyzable esters include, but are not limited to, lower alkyl esters, lower acyloxyalkyl esters (such as acetoxyethyl, acetoxyethyl, aminocarbonyloxyethyl, pivaloyloxyethyl, and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxycarbonyloxyethyl, ethoxycarbonyloxyethyl and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters, and acylamino alkyl esters (such as acetamidomethyl esters). Examples of biohydrolyzable amides include, but are not limited to, lower alkyl amides, α -amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides. Examples of biohydrolyzable carbamates include, but are not limited to, lower alkylamines, substituted

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ethylenediamines, amino acids, hydroxyalkylamines, heterocyclic and heteroaromatic amines, and polyether amines.

The immunomodulatory compound of the invention contains a chiral center, and thus can exist as a racemic mixture of R and S enantiomers. This invention encompasses the use of stereomerically pure forms of this compound, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers may be used in methods and compositions of the invention. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. See, e.g., Jacques, J., et al., *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., et al., *Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E. L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, Ind., 1972).

As used herein and unless otherwise indicated, the term “stereomerically pure” means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound. For example, a stereomerically pure composition of a compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure composition of a compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. As used herein and unless otherwise indicated, the term “stereomerically enriched” means a composition that comprises greater than about 60% by weight of one stereoisomer of a compound, preferably greater than about 70% by weight, more preferably greater than about 80% by weight of one stereoisomer of a compound. As used herein and unless otherwise indicated, the term “enantiomerically pure” means a stereomerically pure composition of a compound having one chiral center. Similarly, the term “stereomerically enriched” means a stereomerically enriched composition of a compound having one chiral center. In other words, the invention encompasses the use of the R or S enantiomer of immunomodulatory compound in the methods.

It should be noted that if there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

5.2 Second Active Agents

An immunomodulatory compound of the invention can be used with or combined with other pharmacologically active compounds (“second active agents or ingredients”) in methods and compositions of the invention. It is believed that certain combinations work synergistically in the treatment of

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particular types of lymphomas. Immunomodulatory compounds of the invention can also work to alleviate adverse effects associated with certain second active agents, and some second active agents can be used to alleviate adverse effects associated with immunomodulatory compounds of the invention.

One or more second active ingredients or agents can be used in the methods and compositions of the invention together with an immunomodulatory compound of the invention. Second active agents can be large molecules (e.g., proteins) or small molecules (e.g., synthetic inorganic, organometallic, or organic molecules).

Examples of large molecule active agents include, but are not limited to, hematopoietic growth factors, cytokines, and monoclonal and polyclonal antibodies. Typical large molecule active agents are biological molecules, such as naturally occurring or artificially made proteins. Proteins that are particularly useful in this invention include proteins that stimulate the survival and/or proliferation of hematopoietic precursor cells and immunologically active poietic cells in vitro or in vivo. Others stimulate the division and differentiation of committed erythroid progenitors in cells in vitro or in vivo. Particular proteins include, but are not limited to: interleukins, such as IL-2 (including recombinant IL-2 ("rIL2")) and canarypox IL-2), IL-10, IL-12, and IL-18; interferons, such as interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon beta-1 a, and interferon gamma-1 b; GM-CSF and GM-CSF; and EPO.

Particular proteins that can be used in the methods and compositions of the invention include, but are not limited to: filgrastim, which is sold in the United States under the trade name Neupogen® (Amgen, Thousand Oaks, Calif.); sargramostim, which is sold in the United States under the trade name Leukine® (Immunex, Seattle, Wash.); and recombinant EPO, which is sold in the United States under the trade name Epogen® (Amgen, Thousand Oaks, Calif.).

Recombinant and mutated forms of GM-CSF can be prepared as described in U.S. Pat. Nos. 5,391,485; 5,393,870; and 5,229,496; all of which are incorporated herein by reference. Recombinant and mutated forms of G-CSF can be prepared as described in U.S. Pat. Nos. 4,810,643; 4,999,291; 5,528,823; and 5,580,755; all of which are incorporated herein by reference.

This invention encompasses the use of native, naturally occurring, and recombinant proteins. The invention further encompasses mutants and derivatives (e.g., modified forms) of naturally occurring proteins that exhibit, in vivo, at least some of the pharmacological activity of the proteins upon which they are based. Examples of mutants include, but are not limited to, proteins that have one or more amino acid residues that differ from the corresponding residues in the naturally occurring forms of the proteins. Also encompassed by the term "mutants" are proteins that lack carbohydrate moieties normally present in their naturally occurring forms (e.g., nonglycosylated forms). Examples of derivatives include, but are not limited to, pegylated derivatives and fusion proteins, such as proteins formed by fusing IgG1 or IgG3 to the protein or active portion of the protein of interest. See, e.g., Penichet, M. L. and Morrison, S. L., *J. Immunol. Methods* 248:91-101 (2001).

Antibodies that can be used in combination with compounds of the invention include monoclonal and polyclonal antibodies. Examples of antibodies include, but are not limited to, trastuzumab (Herceptin®), rituximab (Rituxan®), bevacizumab (Avastin™), pertuzumab (Omnitarg™), tositumomab (Bexxar®), edrecolomab (Panorex®), and G250.

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Compounds of the invention can also be combined with, or used in combination with, anti-TNF- α antibodies.

Large molecule active agents may be administered in the form of anti-cancer vaccines. For example, vaccines that secrete, or cause the secretion of, cytokines such as IL-2, G-CSF, and GM-CSF can be used in the methods, pharmaceutical compositions, and kits of the invention. See, e.g., Emens, L. A., et al., *Curr. Opinion Mol. Ther.* 3(1):77-84 (2001).

In one embodiment of the invention, the large molecule active agent reduces, eliminates, or prevents an adverse effect associated with the administration of an immunomodulatory compound of the invention. Depending on the particular immunomodulatory compound of the invention and the disease or disorder being treated, adverse effects can include, but are not limited to, drowsiness and somnolence, dizziness and orthostatic hypotension, neutropenia, infections that result from neutropenia, increased HIV-viral load, bradycardia, Stevens-Johnson Syndrome and toxic epidermal necrolysis, and seizures (e.g., grand mal convulsions). A specific adverse effect is neutropenia.

Second active agents that are small molecules can also be used to alleviate adverse effects associated with the administration of an immunomodulatory compound of the invention. However, like some large molecules, many are believed to be capable of providing a synergistic effect when administered with (e.g., before, after or simultaneously) an immunomodulatory compound of the invention. Examples of small molecule second active agents include, but are not limited to, anti-cancer agents, antibiotics, immunosuppressive agents, and steroids.

Examples of anti-cancer agents include, but are not limited to: acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; bortezomib (Velcade®); brequinar sodium; bropiramine; busulfan; cactinomycin; calusterone; caracemic; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; celecoxib (COX-2 inhibitor); chlorambucil; cir-olemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofofosine; iproplatin; irinotecan; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lomestr-exol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedopa; mitindomide; mitoxcarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegas-

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pargase; peliomycin; pentamustine; peplomycin sulfate; perfosamide; pipobroman; pipsulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprime; safinol; safinol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spirolatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; taxotere; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triceribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinylicinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; and zorubicin hydrochloride.

Other anti-cancer drugs include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; antidorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; broprimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; capecitabine; carboxamide-amino-triazole; carboxamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetorelix; chlorins; chloroquinoline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatin; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrotidemin B; deslorelin; dexamethasone; dexifosfamide; dextrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxilfluridine; doxorubicin; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; efloimithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofofosine; ilomastat; imatinib

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(e.g., Gleevec®); imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoproc; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; Erbitux, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullin; oblimersen (Genasense®); O⁶-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safinol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; tallimustine; tamoxifen methiodide; taumustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene;

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translation inhibitors; tretinoin; triacetyluridine; tricitabine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatein; zilascorb; and zinstatin stimalamer.

Specific second active agents include, but are not limited to, rituximab, bortezomib, oblimersen (Genasense®), remicade, docetaxel, celecoxib, melphalan, dexamethasone (Decadron®), steroids, gemcitabine, cisplatin, temozolomide, etoposide, cyclophosphamide, temodar, carboplatin, procarbazine, gliadel, tamoxifen, topotecan, methotrexate, Arisa®, taxol, taxotere, fluorouracil, leucovorin, irinotecan, xeloda, CPT-11, interferon alpha, pegylated interferon alpha (e.g., PEG INTRON-A), capecitabine, cisplatin, thiotepa, fludarabine, carboplatin, liposomal daunorubicin, cytarabine, doxetaxol, paclitaxel, vinblastine, IL-2, GM-CSF, dacarbazine, vinorelbine, zoledronic acid, palmitronate, biaxin, busulphan, prednisone, bisphosphonate, arsenic trioxide, vincristine, doxorubicin (Doxil®), paclitaxel, ganciclovir, adriamycin, estramustine sodium phosphate (Emcyt®), sulindac, and etoposide.

5.3 Methods of Treatments and Prevention

Methods of this invention encompass methods of treating, preventing or managing various types of lymphomas. In a preferred embodiment, methods of this invention encompass methods of treating, preventing or managing various types of lymphomas, including but not limited to, mantle cell lymphoma, MCL, lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, follicular lymphoma, and any type of the mantle cell lymphomas that can be seen under the microscope (nodular, diffuse, blastic and mentle zone lymphoma).

As used herein, unless otherwise specified, the term “treating” refers to the administration of a compound of the invention, or other additional active agent, after the onset of symptoms of the particular cancer. As used herein, unless otherwise specified, the term “preventing” refers to the administration prior to the onset of symptoms, particularly to patients at risk of cancer, and in particular lymphoma. The term “prevention” includes the inhibition of a symptom of the particular cancer. Patients with familial history of cancer or lymphoma in particular are preferred candidates for preventive regimens. As used herein and unless otherwise indicated, the term “managing” encompasses preventing the recurrence of the particular cancer in a patient who had suffered from it, lengthening the time a patient who had suffered from the cancer remains in remission, and/or reducing mortality rates of the patients.

As used herein, the term “cancer” includes, but is not limited to, solid tumors and blood born tumors. The term “cancer” refers to disease of skin tissues, organs, blood, and vessels, including, but not limited to, cancers of the bladder, bone or blood, brain, breast, cervix, chest, colon, endometrium, esophagus, eye, head, kidney, liver, lymph nodes, lung, mouth, neck, ovaries, pancreas, prostate, rectum, stomach, testis, throat, and uterus.

The term “lymphoma” refers a heterogenous group of neoplasms arising in the reticuloendothelial and lymphatic systems. Non-Hodgkin’s lymphoma (NHL) refers to malignant monoclonal proliferation of lymphoid cells in sites of the

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immune system, including lymph nodes, bone marrow, spleen, liver and gastrointestinal tract. The NHL includes, but is not limited to, mantle cell lymphoma, MCL, lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, follicular lymphoma, and any type of the mantle cell lymphomas that can be seen under the microscope (nodular, diffuse, blastic and mentle zone lymphoma).

The term “relapsed” refers to a situation where patients who have had a remission of cancer after therapy have a return of lymphoid cells in the immune systems. The term “refractory or resistant” refers to a circumstance where patients, even after intensive treatment, have residual lymphoid cells in the immune systems.

This invention encompasses methods of treating patients who have been previously treated for cancer, but are non-responsive to standard therapies, as well as those who have not previously been treated. The invention also encompasses methods of treating patients regardless of patient’s age, although some cancers are more common in certain age groups. The invention further encompasses methods of treating patients who have undergone surgery in an attempt to treat the cancer at issue, as well as those who have not. Because patients with cancer have heterogenous clinical manifestations and varying clinical outcomes, the treatment given to a patient may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation specific secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual patient with cancer.

Methods encompassed by this invention comprise administering one or more immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (e.g., hydrate), stereoisomer, clathrate, or prodrug thereof, to a patient (e.g., a human) suffering, or likely to suffer, from cancer, particularly mantle cell lymphoma.

In one embodiment of the invention, an immunomodulatory compound of the invention can be administered orally and in single or divided daily doses in an amount of from about 0.10 to about 150 mg/day. In a preferred embodiment, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) may be administered in an amount of from about 0.10 to 150 mg per day, from about 1 to about 50 mg per day, or from about 5 to about 25 mg per day. Specific doses per day include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 mg per day.

In a preferred embodiment, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) may be administered in an amount of from about 1 to 50 mg per day, or from about 5 to about 25 mg per day to patients with various types of non-Hodgkin’s lymphomas such as mantle cell lymphoma, MCL, lymphocytic lymphoma of intermediate differentiation, intermediate lymphocytic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, diffuse large cell lymphoma, follicular lymphoma, and mentle zone lymphoma.

In particular, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) may be administered to patients with mantle cell lymphoma in an amount of from about 1 to 50 mg per day, or from about 5 to about 25 mg per day. In a specific embodiment, 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) may be

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administered to patients with mantle cell lymphoma in an amount of about 10, 15, 20, 25 or 50 mg per day. In a specific embodiment, Revlimid® can be administered in an amount of about 25 mg per day to patients with mantle cell lymphoma.

In one embodiment, the recommended starting dose of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) is 10 mg per day. The dose can be escalated every week to 15, 20, 25, 30, 35, 40, 45 and 50 mg per day. The patients who are dosed initially at 10 mg and who experience thrombocytopenia or neutropenia that develops within or after the first four weeks of starting Revlimid® therapy may have their dosage adjusted according to a platelet count or absolute neutrophil count (ANC).

5.3.1 Combination Therapy with a Second Active Agent

Specific methods of the invention comprise administering an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (e.g., hydrate), stereoisomer, clathrate, or prodrug thereof, in combination with one or more second active agents, and/or in combination with radiation therapy, blood transfusions, or surgery. Examples of immunomodulatory compounds of the invention are disclosed herein (see, e.g., section 4.1). Examples of second active agents are also disclosed herein (see, e.g., section 4.2).

Administration of an immunomodulatory compound of the invention and the second active agents to a patient can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. A preferred route of administration for an immunomodulatory compound of the invention is orally. Preferred routes of administration for the second active agents or ingredients of the invention are known to those of ordinary skill in the art. See, e.g., *Physicians' Desk Reference*, (2006).

In one embodiment of the invention, the second active agent is administered intravenously or subcutaneously and once or twice daily in an amount of from about 1 to about 1,000 mg, from about 5 to about 500 mg, from about 10 to about 375 mg, or from about 50 to about 200 mg. The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of disease, and the amount(s) of immunomodulatory compounds of the invention and any optional additional active agents concurrently administered to the patient. In a particular embodiment, the second active agent is rituximab, bortezomib, oblimersen (Genasense®), GM-CSF, G-CSF, EPO, taxotere, irinotecan, dacarbazine, transretinoic acid, topotecan, pentoxifylline, ciprofloxacin, dexamethasone, vincristine, doxorubicin, COX-2 inhibitor, IL2, IL8, IL18, IFN, Ara-C, vinorelbine, or a combination thereof.

In a specific embodiment, an immunomodulatory compound of the invention is administered in combination with rituximab to patients with mantle cell lymphomas. In a specific embodiment, Revlimid® is administered to patients with mantle cell lymphoma in an amount of from about 5 to about 25 mg per day in combination with rituximab in an amount of 375 mg/m² by intravenous infusion weekly.

In a preferred embodiment, Revlimid® is administered alone or in combination with rituximab to patients with various types of non-Hodgkin's lymphomas, including, but not limited to, mantle cell lymphoma, MCL, lymphocytic lymphoma of intermediate differentiation, intermediate lympho-

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cyclic lymphoma, ILL, diffuse poorly differentiated lymphocytic lymphoma, PDL, centrocytic lymphoma, diffuse small-cleaved cell lymphoma, DSCCL, diffuse large cell lymphoma, follicular lymphoma, and mantle zone lymphoma.

In another embodiment, an immunomodulatory compound of the invention is administered alone or in combination with a second active ingredient such as vinblastine or fludarabine to patients with various types of lymphomas, including, but not limited to, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma or relapsed or refractory low grade follicular lymphoma.

In another embodiment, GM-CSF, G-CSF or EPO is administered subcutaneously during about five days in a four or six week cycle in an amount of from about 1 to about 750 mg/m²/day, preferably in an amount of from about 25 to about 500 mg/m²/day, more preferably in an amount of from about 50 to about 250 mg/m²/day, and most preferably in an amount of from about 50 to about 200 mg/m²/day. In a certain embodiment, GM-CSF may be administered in an amount of from about 60 to about 500 mcg/m² intravenously over 2 hours, or from about 5 to about 12 mcg/m²/day subcutaneously. In a specific embodiment, G-CSF may be administered subcutaneously in an amount of about 1 mcg/kg/day initially and can be adjusted depending on rise of total granulocyte counts. The maintenance dose of G-CSF may be administered in an amount of about 300 (in smaller patients) or 480 mcg subcutaneously. In a certain embodiment, EPO may be administered subcutaneously in an amount of 10,000 Unit 3 times per week.

This invention also encompasses a method of increasing the dosage of an anti-cancer drug or agent that can be safely and effectively administered to a patient, which comprises administering to a patient (e.g., a human) an immunomodulatory compound of the invention, or a pharmaceutically acceptable derivative, salt, solvate (e.g., hydrate), or prodrug thereof. Patients that can benefit by this method are those likely to suffer from an adverse effect associated with anti-cancer drugs for treating a specific cancer of the blood, skin, subcutaneous tissue, lymph nodes, brain, lung, liver, bone, intestine, colon, heart, pancreas, adrenal, kidney, prostate, breast, colorectal, or combinations thereof. The administration of an immunomodulatory compound of the invention alleviates or reduces adverse effects which are of such severity that it would otherwise limit the amount of anti-cancer drug.

In one embodiment, an immunomodulatory compound of the invention can be administered orally and daily in an amount of from about 0.10 to about 150 mg, and preferably from about 1 to about 50 mg, more preferably from about 5 to about 25 mg prior to, during, or after the occurrence of the adverse effect associated with the administration of an anti-cancer drug to a patient. In a particular embodiment, an immunomodulatory compound of the invention is administered in combination with specific agents such as heparin, aspirin, coumadin, or G-CSF to avoid adverse effects that are associated with anti-cancer drugs such as but not limited to neutropenia or thrombocytopenia.

In another embodiment, this invention encompasses a method of treating, preventing and/or managing lymphoma, which comprises administering an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (e.g., hydrate), stereoisomer, clathrate, or prodrug thereof, in conjunction with (e.g., before, during, or after) conventional therapy including, but not limited to, surgery, immunotherapy, biological therapy, radiation therapy, or

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other non-drug based therapy presently used to treat, prevent or manage cancer. The combined use of the immunomodulatory compounds of the invention and conventional therapy may provide a unique treatment regimen that is unexpectedly effective in certain patients. Without being limited by theory, it is believed that immunomodulatory compounds of the invention may provide additive or synergistic effects when given concurrently with conventional therapy.

As discussed elsewhere herein, the invention encompasses a method of reducing, treating and/or preventing adverse or undesired effects associated with conventional therapy including, but not limited to, surgery, chemotherapy, radiation therapy, hormonal therapy, biological therapy and immunotherapy. An immunomodulatory compound of the invention and other active ingredient can be administered to a patient prior to, during, or after the occurrence of the adverse effect associated with conventional therapy.

In one embodiment, an immunomodulatory compound of the invention can be administered in an amount of from about 0.10 to about 150 mg, and preferably from about 1 to about 50 mg, more preferably from about 5 to about 25 mg orally and daily alone, or in combination with a second active agent disclosed herein (see, e.g., section 4.2), prior to, during, or after the use of conventional therapy.

5.3.2 Use with Transplantation Therapy

Compounds of the invention can be used to reduce the risk of Graft Versus Host Disease (GVHD). Therefore, the invention encompasses a method of treating, preventing and/or managing cancer, which comprises administering the immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (e.g., hydrate), stereoisomer, clathrate, or prodrug thereof, in conjunction with transplantation therapy.

As those of ordinary skill in the art are aware, the treatment of cancer is often based on the stages and mechanism of the disease. For example, as inevitable leukemic transformation develops in certain stages of cancer, transplantation of peripheral blood stem cells, hematopoietic stem cell preparation or bone marrow may be necessary. The combined use of the immunomodulatory compound of the invention and transplantation therapy provides a unique and unexpected synergism. In particular, an immunomodulatory compound of the invention exhibits immunomodulatory activity that may provide additive or synergistic effects when given concurrently with transplantation therapy in patients with cancer.

An immunomodulatory compound of the invention can work in combination with transplantation therapy reducing complications associated with the invasive procedure of transplantation and risk of GVHD. This invention encompasses a method of treating, preventing and/or managing cancer which comprises administering to a patient (e.g., a human) an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (e.g., hydrate), stereoisomer, clathrate, or prodrug thereof, before, during, or after the transplantation of umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow. Examples of stem cells suitable for use in the methods of the invention are disclosed in U.S. patent publication nos. 2002/0123141, 2003/0235909 and 2003/0032179, by R. Hariri et al., the entireties of which are incorporated herein by reference.

In one embodiment of this method, an immunomodulatory compound of the invention is administered to patients with lymphomas before, during, or after the transplantation of autologous peripheral blood progenitor cell.

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In another embodiment, an immunomodulatory compound of the invention is administered to patients with relapsed lymphoma after the stem cell transplantation.

5.3.3 Cycling Therapy

In certain embodiments, the prophylactic or therapeutic agents of the invention are cyclically administered to a patient. Cycling therapy involves the administration of an active agent for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

Consequently, in one specific embodiment of the invention, an immunomodulatory compound of the invention is administered daily in a single or divided doses in a four to six week cycle with a rest period of about a week or two weeks. The invention further allows the frequency, number, and length of dosing cycles to be increased. Thus, another specific embodiment of the invention encompasses the administration of an immunomodulatory compound of the invention for more cycles than are typical when it is administered alone. In yet another specific embodiment of the invention, an immunomodulatory compound of the invention is administered for a greater number of cycles that would typically cause dose-limiting toxicity in a patient to whom a second active ingredient is not also being administered.

In one embodiment, an immunomodulatory compound of the invention is administered daily and continuously for three or four weeks at a dose of from about 0.10 to about 150 mg/d followed by a break of one or two weeks. In a particular embodiment, an immunomodulatory compound of the invention is administered in an amount of from about 1 to about 50 mg/day, preferably in an amount of about 25 mg/day for three to four weeks, followed by one week or two weeks of rest in a four or six week cycle.

In a preferred embodiment, 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) is administered to patients with various types of lymphomas such as mantle cell lymphoma, follicular lymphoma and diffuse large cell lymphoma, in an amount of about 10 mg, 15 mg, 20 mg, 25 mg or 30 mg per day for 21 days followed by seven days rest in a 28 day cycle. In the most preferred embodiment, 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) is administered to patients with refractory or relapsed mantle cell lymphoma in an amount of about 25 mg per day for 21 days followed by seven days rest in a 28 day cycle.

In one embodiment of the invention, an immunomodulatory compound of the invention and a second active agent or ingredient are administered orally, with administration of an immunomodulatory compound of the invention occurring 30 to 60 minutes prior to a second active ingredient, during a cycle of four to six weeks. In another embodiment of the invention, an immunomodulatory compound of the invention is administered orally and a second active ingredient is administered by intravenous infusion.

In a specific embodiment, one cycle comprises the administration of from about 10 to about 25 mg/day of Revlimid® and from about 50 to about 750 mg/m²/day of a second active ingredient daily for three to four weeks and then one or two weeks of rest.

In one embodiment, rituximab can be administered in an amount of 375 mg/m² as an additional active agent to patients with various types of lymphomas such as mantle cell lymphoma.

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phoma, follicular lymphoma and diffuse large cell lymphoma. In a preferred embodiment, rituximab can be administered in an amount of 375 mg/m² as an additional active agent to patients with refractory or relapsed mantle cell lymphoma. In a preferred embodiment, one cycle comprises the administration of Revlimid® given orally daily for 21 days followed by 7 days of rest and 375 mg/m² of rituximab by intravenous infusion weekly for four weeks.

Typically, the number of cycles during which the combinatorial treatment is administered to a patient will be from about one to about 24 cycles, more typically from about two to about 16 cycles, and even more typically from about four to about three cycles.

5.4 Pharmaceutical Compositions and Dosage Forms

Pharmaceutical compositions can be used in the preparation of individual, single unit dosage forms. Pharmaceutical compositions and dosage forms of the invention comprise an immunomodulatory compound of the invention, or a pharmaceutically acceptable salt, solvate (e.g., hydrate), stereoisomer, clathrate, or prodrug thereof. Pharmaceutical compositions and dosage forms of the invention can further comprise one or more excipients.

Pharmaceutical compositions and dosage forms of the invention can also comprise one or more additional active ingredients. Consequently, pharmaceutical compositions and dosage forms of the invention comprise the active ingredients disclosed herein (e.g., an immunomodulatory compound of the invention and a second active agent). Examples of optional second, or additional, active ingredients are disclosed herein (see, e.g., section 5.2).

Single unit dosage forms of the invention are suitable for oral, mucosal (e.g., nasal, sublingual, vaginal, buccal, or rectal), parenteral (e.g., subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical (e.g., eye drops or other ophthalmic preparations), transdermal or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; eye drops or other ophthalmic preparations suitable for topical administration; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease may contain larger amounts of one or more of the active ingredients it comprises than a dosage form used in the chronic treatment of the same disease. Similarly, a parenteral dosage form may contain smaller amounts of one or more of the active ingredients it comprises than an oral dosage form used to treat the same disease. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, e.g., *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton Pa. (1990).

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-

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limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, this invention encompasses pharmaceutical compositions and dosage forms that contain little, if any, lactose or other mono- or disaccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient.

Lactose-free compositions of the invention can comprise excipients that are well known in the art and are listed, for example, in the *U.S. Pharmacopeia* (USP) 25-NF20 (2002). In general, lactose-free compositions comprise active ingredients, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Preferred lactose-free dosage forms comprise active ingredients, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, N.Y., 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs, and strip packs.

The invention further encompasses pharmaceutical compositions and dosage forms that comprise one or more compounds that reduce the rate by which an active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers.

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Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise an immunomodulatory compound of the invention or a pharmaceutically acceptable salt, solvate (e.g., hydrate), stereoisomer, clathrate, or prodrug thereof in an amount of from about 0.10 to about 150 mg. Typical dosage forms comprise an immunomodulatory compound of the invention or a pharmaceutically acceptable salt, solvate (e.g., hydrate), stereoisomer, clathrate, or prodrug thereof in an amount of about 0.1, 1, 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 25, 50, 100, 150 or 200 mg. In a specific embodiment, a preferred dosage form comprises 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) in an amount of about 1, 2.5, 5, 10, 15, 20, 25 or 50 mg. Typical dosage forms comprise the second active ingredient in an amount of 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. Of course, the specific amount of the anti-cancer drug will depend on the specific agent used, the type of cancer being treated or managed, and the amount(s) of an immunomodulatory compound of the invention and any optional additional active agents concurrently administered to the patient.

5.4.1 Oral Dosage Forms

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to, tablets (e.g., chewable tablets), caplets, capsules, and liquids (e.g., flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing, Easton Pa. (1990).

In one embodiment, a preferred dosage form is a capsule or tablet comprising 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) in an amount of about 1, 2.5, 5, 10, 15, 20, 25 or 50 mg. In a specific embodiment, a preferred capsule or tablet dosage form comprises 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (Revlimid®) in an amount of about 5 or 10 mg.

Typical oral dosage forms of the invention are prepared by combining the active ingredients in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid excipients are employed. If desired, tablets can be coated by standard aqueous or nonaqueous techniques. Such dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredients with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

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For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredients in a free-flowing form such as powder or granules, optionally mixed with an excipient. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103 AVICEL RC-581, AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa.), and mixtures thereof. A specific binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants are used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other alginates, other celluloses, gums, and mixtures thereof.

Lubricants that can be used in pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil),

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zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL200, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

A preferred solid oral dosage form of the invention comprises an immunomodulatory compound of the invention, anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

5.4.2 Delayed Release Dosage Forms

Active ingredients of the invention can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (e.g., adverse) effects.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

5.4.3 Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes including, but not limited to, subcutaneous,

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intravenous (including bolus injection), intramuscular, and intraarterial. Because their administration typically bypasses patients' natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, but are not limited to: Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active ingredients disclosed herein can also be incorporated into the parenteral dosage forms of the invention. For example, cyclodextrin and its derivatives can be used to increase the solubility of an immunomodulatory compound of the invention and its derivatives. See, e.g., U.S. Pat. No. 5,134,127, which is incorporated herein by reference.

6. EXAMPLES

Certain embodiments of the invention are illustrated by the following non-limiting example.

6.1 Clinical Studies in Patients

6.1.1 Treatment of Mantle Cell Lymphomas

A single-center, open label, phase I/II study was conducted to determine the maximum tolerated dose (MTD) and to evaluate the efficacy of 3-(4-amino-1-oxo-1,3-dihydro-isoin-
dol-2-yl)-piperidin-2,6-dione (lenalidomide or Revlimid®) in combination with rituximab for relapsed or refractory mantle cell lymphoma (MCL). Patients with one to four lines of prior therapy were eligible. Patients with prior treatment using thalidomide or rituximab, regardless of resistance, were eligible. Each cycle (28 days) of treatment comprises administration of 3-(4-amino-1-oxo-1,3-dihydro-isoin-
dol-2-yl)-piperidin-2,6-dione (Revlimid®) given orally daily for 21 days followed by 7 days of rest and 375 mg/m² of rituximab by intravenous infusion weekly for four weeks. A standard phase I dose escalation was used to determine MTD with dose levels at 10 mg, 15 mg, 20 mg, and 25 mg of Revlimid®. Dose-limiting toxicity (DLT) was defined as grade 3 or 4 non-hematologic or grade 4 hematologic toxicity during the first cycle.

Ten patients were enrolled with seven evaluable. Median age was 73, range 56-84; median prior lines of therapy were 3, range 1-4. Each cohort had 3 patients. No DLT was encountered and maximum dose of Revlimid® was up to 20 mg. The number of cycles given ranged from one to five cycles. There were no grade 3 or 4 toxicities during the cycle. Grade 1 non-hematologic toxic events included fatigue in 4, stomatitis in 3, pruritis in 3, and myalgias in 2. Grade 2 non-hematologic toxic events included rash in 2 and myalgias in 2. Grade 1 hematologic events included leukopenia in 3, thrombocytopenia in 2 and anemia in 1. There was one episode of grade 2 anemia. Beyond the first cycle, there was only 1 grade 3

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toxicity (thrombocytopenia) during cycle 2. Therefore, the MTD has not been reached. Two patients had stable disease at cycle 3 and cycle 5, respectively. Four patients had progressive disease and were taken off the study. One patient progressed in the first cycle.

The study result shows that Revlimid® is effective in treating mantle cell lymphoma, particularly relapsed or refractory mantle cell lymphoma.

6.1.2 Treatment of Aggressive NHL

A multi-center, open-label, Phase II study was conducted in patients with relapsed and refractory aggressive non-Hodgkin's lymphoma (NHL). The trial was designed to evaluate the therapeutic potential and safety of oral monotherapy with 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidin-2,6-dione (Revlimid® or lenalidomide) in 40 patients with relapsed and refractory aggressive NHL following one or more prior treatment regimen with measurable disease. Patients in the study received lenalidomide in an amount of 25mg orally once daily for days one to 21 in a 28-day cycle and continued therapy for 52 weeks as tolerated or until disease progression.

Twenty-five patients age 45 to 80 years (median age 63), with relapsed and refractory aggressive NHL, and who had received a median of 2.5 prior treatments (range: 1-6 prior treatments), were administered with lenalidomide in an amount of 25 mg orally once daily for 21 days in the treatment cycle. Sixteen patients with aggressive NHL were evaluable for tumour assessment. Of the 16 patients, eight had diffuse large cell lymphoma, three had mantle cell lymphoma, two patients had follicular lymphoma, one had transformed lymphoma, and two had aggressive lymphoma of unknown histology.

There were five (31 per cent) patients who experienced objective responses to lenalidomide monotherapy. One patient achieved complete response and four patients achieved partial responses. One patient with diffuse large cell lymphoma achieved complete response with progression free survival of more than 180 days. One patient with diffuse large cell lymphoma achieved partial response with progression free survival for 135 days. One patient with diffuse large cell lymphoma achieved partial response with progression free survival for 242 days. One patient with follicular lymphoma achieved partial response with progression free survival for more than 55 days. One patient with mantle cell lymphoma achieved partial response with progression free survival for more than 57 days. Four patients exhibited stable disease. Seven patients had disease progression after a median follow-up of two months (range one to seven months).

Grade 3 and 4 adverse events occurred in ten of 22 patients. These were predominately haematological and Grade 3 adverse reaction, with only three patients experiencing a Grade 4 adverse reaction.

The embodiments of the invention described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the invention and are encompassed by the appended claims.

What is claimed is:

1. A method of treating mantle cell lymphoma in a human, which comprises (a) administering to a human having mantle cell lymphoma from about 5 mg to about 25 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione or a pharmaceutically acceptable salt or hydrate

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thereof for 21 days followed by seven days rest in a 28 day cycle; and (b) repeating step (a), wherein the mantle cell lymphoma is relapsed, refractory, or relapsed and refractory to conventional therapy.

2. The method of claim 1, wherein the amount of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is about 5, 10, 15, 20 or 25 mg per day.

3. The method of claim 2, wherein the amount of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is about 10, 15, 20, or 25 mg per day.

4. The method of claim 3, wherein the amount of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is about 25 mg per day.

5. The method of claim 2, wherein 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is enantiomerically pure.

6. The method of claim 5, wherein 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is S enantiomer.

7. The method of claim 5, wherein 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is R enantiomer.

8. The method of claim 2, wherein 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is administered orally.

9. The method of claim 8, wherein 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is administered in the form of a capsule or tablet.

10. The method of claim 1, further comprising administration of rituximab in an amount of 375 mg/m² by intravenous infusion weekly.

11. A method of treating mantle cell lymphoma, which comprises (a) administering to a patient having mantle cell lymphoma from about 5 mg to about 25 mg per day of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione or a pharmaceutically acceptable salt or hydrate thereof for 21 days followed by a seven days rest in a 28 day cycle; (b) repeating step (a); (c) administering to the patient a therapeutically effective amount of a second active agent selected from a hematopoietic growth factor, a cytokine, an anticancer agent, an antibiotic, a cox-2 inhibitor, a corticosteroid, rituximab, or a combination thereof for a period of time followed by a period of rest; and (d) repeating step (c), wherein the mantle cell lymphoma is relapsed, refractory, or relapsed and refractory to conventional therapy.

12. The method of claim 11, wherein the second active agent is rituximab.

13. The method of claim 11, wherein the second active agent is dexamethasone.

14. The method of claim 11, wherein the second active agent is prednisone.

15. The method of claim 1 or 11, wherein the amount of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is about 5 mg to about 25 mg per day.

16. The method of claim 15, wherein the amount of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is about 5 mg per day.

17. The method of claim 15, wherein the amount of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is about 10 mg per day.

18. The method of claim 15, wherein the amount of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is about 15 mg per day.

19. The method of claim 15, wherein the amount of 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione administered is about 20 mg per day.

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20. The method of claim 15, wherein the amount of 3-(4-amino-oxo-1,3-dihydro-isindol-2-yl)-piperidine-2,6-dione administered is about 25 mg per day.

21. The method of claim 11, wherein 3-(4-amino-oxo-1,3-dihydro-isindol-2-yl)-piperidine-2,6-dione is administered orally.

22. The method of claim 21, wherein 3-(4-amino-oxo-1,3-dihydro-isindol-2-yl)-piperidine-2,6-dione is administered in the form of a capsule or tablet.

23. The method of claim 12, wherein the rituximab is administered in an amount of 375 mg/m² by intravenous infusion weekly.

24. The method of claim 11, wherein the anticancer agent is a proteasome inhibitor.

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